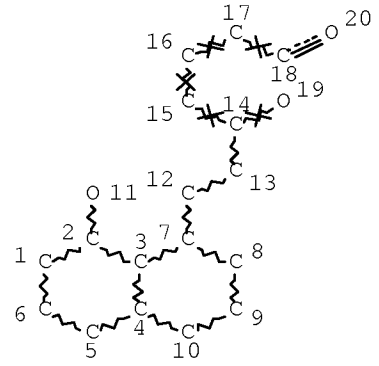
```
=> d que stat l3
L1              STR
```



```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE
L3         5368 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED  144001 ITERATIONS                              5368 ANSWERS
SEARCH TIME: 00.00.01


=> d his ful

     (FILE 'HOME' ENTERED AT 16:06:41 ON 22 JUN 2009)

     FILE 'STNGUIDE' ENTERED AT 16:06:44 ON 22 JUN 2009

     FILE 'STNGUIDE' ENTERED AT 16:07:09 ON 22 JUN 2009

     FILE 'LREGISTRY' ENTERED AT 16:07:19 ON 22 JUN 2009
L1              STR

     FILE 'REGISTRY' ENTERED AT 16:08:29 ON 22 JUN 2009
L2           50 SEA SSS SAM L1

     FILE 'STNGUIDE' ENTERED AT 16:08:49 ON 22 JUN 2009
                D QUE STAT

     FILE 'REGISTRY' ENTERED AT 16:11:00 ON 22 JUN 2009
L3         5368 SEA SSS FUL L1
                SAVE TEMP L3 CHA122PSET1/A

     FILE 'STNGUIDE' ENTERED AT 16:11:25 ON 22 JUN 2009

     FILE 'ZCAPLUS' ENTERED AT 16:12:27 ON 22 JUN 2009
```

```
                E US2007-576122/APPS

     FILE 'HCAPLUS' ENTERED AT 16:12:49 ON 22 JUN 2009
L4             1 SEA SPE=ON  ABB=ON  PLU=ON  US2007-576122/APPS
                D SCAN
                SAVE TEMP L4 CHA122HCAAPP/A

     FILE 'STNGUIDE' ENTERED AT 16:13:15 ON 22 JUN 2009

     FILE 'WPIX' ENTERED AT 16:13:22 ON 22 JUN 2009
L5             1 SEA SPE=ON  ABB=ON  PLU=ON  US2007-576122/APPS
                D IALL CODE L5

     FILE 'STNGUIDE' ENTERED AT 16:14:26 ON 22 JUN 2009

     FILE 'REGISTRY' ENTERED AT 16:14:37 ON 22 JUN 2009

     FILE 'HCAPLUS' ENTERED AT 16:14:45 ON 22 JUN 2009
7L6              TRA PLU=ON  L4 1- RN :      30 TERMS

     FILE 'REGISTRY' ENTERED AT 16:14:45 ON 22 JUN 2009
L7            30 SEA SPE=ON  ABB=ON  PLU=ON  L6
                SAVE TEMP L7 CHA122REGAPP/A

     FILE 'STNGUIDE' ENTERED AT 16:15:07 ON 22 JUN 2009

     FILE 'WPIX' ENTERED AT 16:15:22 ON 22 JUN 2009
                SAVE TEMP L5 CHA122WPIAPP/A

     FILE 'STNGUIDE' ENTERED AT 16:15:37 ON 22 JUN 2009

     FILE 'REGISTRY' ENTERED AT 16:16:36 ON 22 JUN 2009
L8            12 SEA SPE=ON  ABB=ON  PLU=ON  L7 NOT L3
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 16:17:39 ON 22 JUN 2009

     FILE 'LREGISTRY' ENTERED AT 16:19:48 ON 22 JUN 2009
L9              STR
                SAVE TEMP L9 CHA122PSTRA/Q
L10             STR L9
                SAVE TEMP L10 CHA122PSTRB/Q
L11             STR L9
                SAVE TEMP L11 CHA122PSTRC/Q
L12             STR L9
                SAVE TEMP L12 CHA122PSTRD/Q
L13             STR L12
                SAVE TEMP L13 CHA122PSTRE/Q

     FILE 'STNGUIDE' ENTERED AT 16:26:43 ON 22 JUN 2009
                D QUE STAT L3


     FILE HOME

     FILE STNGUIDE
     FILE CONTAINS CURRENT INFORMATION.
     LAST RELOADED: Jun 19, 2009 (20090619/UP).

     FILE LREGISTRY
```

LREGISTRY IS A STATIC LEARNING FILE

CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 21 JUN 2009 HIGHEST RN 1159253-26-5
DICTIONARY FILE UPDATES: 21 JUN 2009 HIGHEST RN 1159253-26-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 9, 2009.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

FILE ZCAPLUS

FILE COVERS 1907 - 22 Jun 2009 VOL 150 ISS 26
FILE LAST UPDATED: 21 Jun 2009 (20090621/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2009

ZCAplus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE HCAPLUS

databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 22 Jun 2009 VOL 150 ISS 26
FILE LAST UPDATED: 21 Jun 2009 (20090621/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2009

HCAplus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE WPIX
FILE LAST UPDATED: 19 JUN 2009 <20090619/UP>
MOST RECENT UPDATE: 200939 <200939/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE
>>> Now containing more than 1.4 million chemical structures in DCR <<<

>>> IPC, ECLA and US National Classifications have been updated
with reclassifications to March 15th, 2009.
F-Term and FI-Term original classifications are current and
reclassification will commence in June.
No update date (UP) has been created for the reclassified
documents, but they can be identified by
specific update codes (see HELP CLA for details)<<<

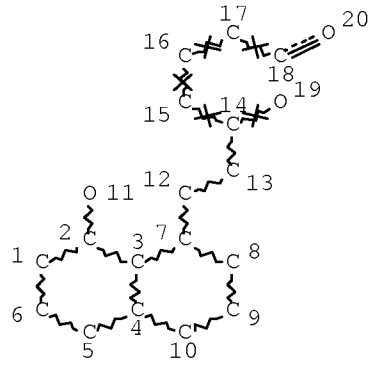
FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.com/stn_guide.html

FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomsonreuters.com/support/patents/coverage/latestupdate

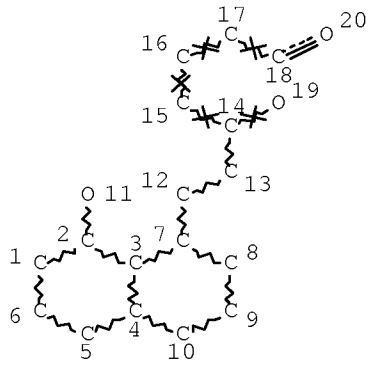
EXPLORE DERWENT WORLD PATENTS INDEX IN STN ANAVIST, VERSION 2.0:
http://www.stn-international.com/DWPIAnaVist2_0608.html

>>> HELP for European Patent Classifications see HELP ECLA, HELP ICO <<<

```
=> => d que stat l7
L6              STR
```



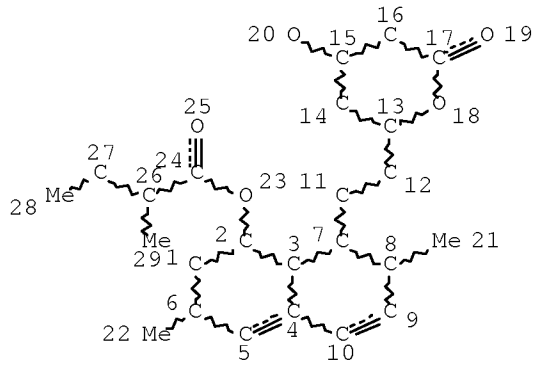
```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE
L7         5368 SEA FILE=REGISTRY SSS FUL L6

100.0% PROCESSED  144001 ITERATIONS                          5368 ANSWERS
SEARCH TIME: 00.00.01


=> d que stat l9
L3  (          1)SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  US2007-576122/APPS
L4                SEL  PLU=ON  L3 1- RN :      30 TERMS
L5            30 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L4
L8             9 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L5 AND MAN/CI
L9             3 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L8 NOT SEQUENCE/FS


=> d que stat l15
L6              STR
```



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L7 5368 SEA FILE=REGISTRY SSS FUL L6
L13 STR



NODE ATTRIBUTES:
CONNECT IS E1 RC AT 20
CONNECT IS E3 RC AT 26
CONNECT IS E2 RC AT 27
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

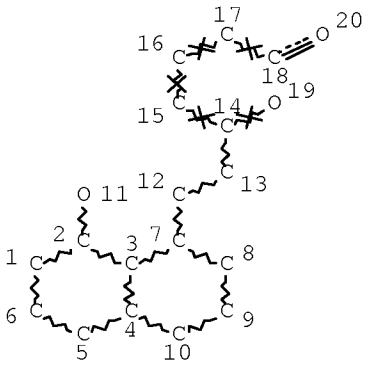
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE
L15 199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13

100.0% PROCESSED 3321 ITERATIONS 199 ANSWERS

SEARCH TIME: 00.00.01

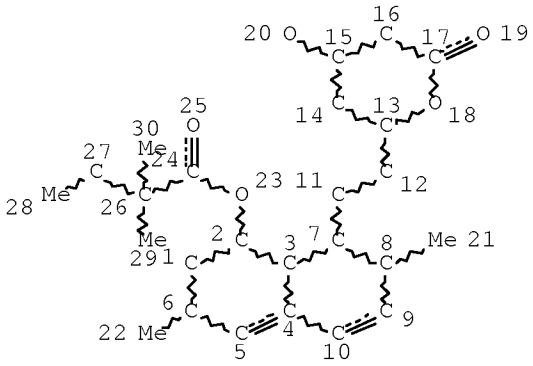
=> d que stat l18
L6 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L7 5368 SEA FILE=REGISTRY SSS FUL L6
L16 STR



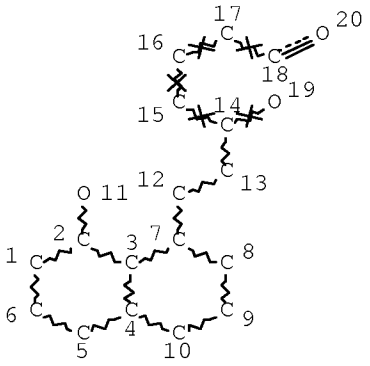
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 20
CONNECT IS E2 RC AT 27
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 30

STEREO ATTRIBUTES: NONE
L18 202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16

100.0% PROCESSED 1569 ITERATIONS 202 ANSWERS
SEARCH TIME: 00.00.15

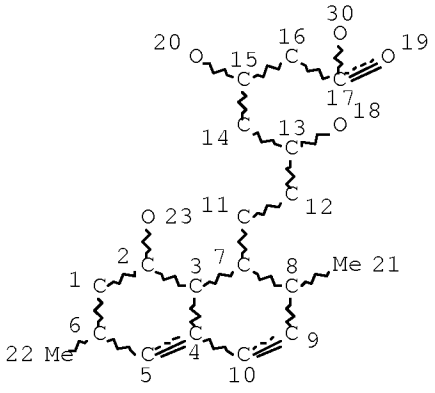
=> d que stat l22
L6 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L7 5368 SEA FILE=REGISTRY SSS FUL L6
L20 STR



NODE ATTRIBUTES:
CONNECT IS E1 RC AT 18
CONNECT IS E1 RC AT 20

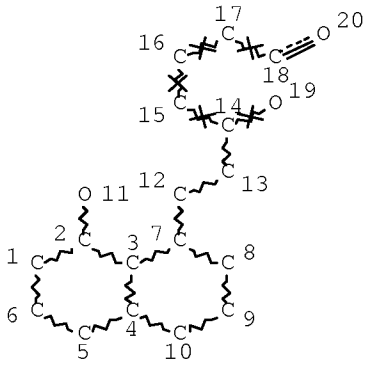
CONNECT IS E1 RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE
L22   18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20

100.0% PROCESSED   1714 ITERATIONS   18 ANSWERS
SEARCH TIME: 00.00.01

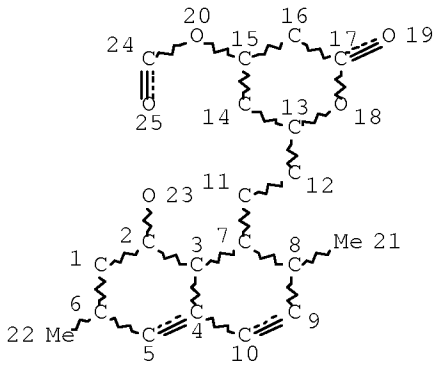
=> d que stat l26
L6   STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L7   5368 SEA FILE=REGISTRY SSS FUL L6
L24   STR



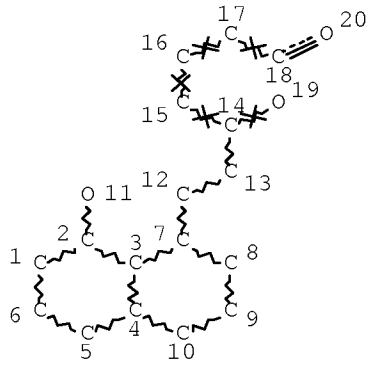
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
L26   5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24

100.0% PROCESSED   2213 ITERATIONS   5 ANSWERS
SEARCH TIME: 00.00.01

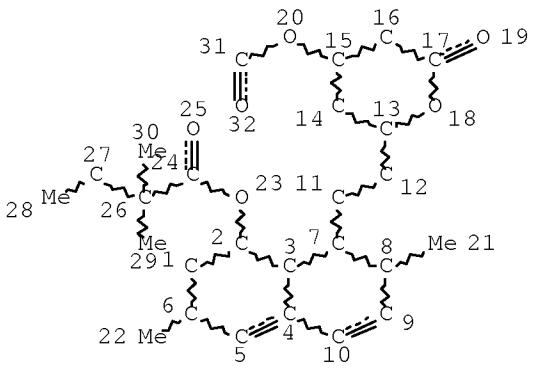
=> d que stat l30
L6   STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L7   5368 SEA FILE=REGISTRY SSS FUL L6
L28   STR



NODE ATTRIBUTES:
CONNECT IS E2 RC AT 27
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE
L30   800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28

100.0% PROCESSED   1569 ITERATIONS   800 ANSWERS
SEARCH TIME: 00.00.01

=> d que nos l73
L6   STR
L7   5368 SEA FILE=REGISTRY SSS FUL L6
L20   STR
L22   18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24   STR
L26   5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28   STR
L30   800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L73   823 SEA FILE=REGISTRY SPE=ON ABB=ON PLU=ON L22 OR L26 OR L30

=> d que nos l82
L6   STR
L7   5368 SEA FILE=REGISTRY SSS FUL L6
L13   STR
L15   199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16   STR
L18   202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L20   STR
L22   18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24   STR
L26   5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28   STR
L30   800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L31   QUE SPE=ON ABB=ON PLU=ON MORGAN, B?/AU,AUTH

```
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L73         823 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 OR L26 OR L30
L74          59 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L18/PRO
L75          67 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L15/NPRO
L76          34 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L74 AND L75
L77           8 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L22
L78           6 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L76 AND L77
L79           9 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L73
L80           6 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L78 AND L79
L81           1 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L80 AND (L31 OR L32
                OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L82           5 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L80 NOT L81


=> d que nos l72
L3  (         1)SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  US2007-576122/APPS
L4              SEL  PLU=ON  L3 1- RN :      30 TERMS
L5           30 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L4
L6              STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L8            9 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L5 AND MAN/CI
L9            3 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L8 NOT SEQUENCE/FS
L13             STR
L15         199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16             STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L20             STR
L22          18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24             STR
L26           5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28             STR
L30         800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L48             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLYSIS+PFT,OLD,NEW,NT/CT
```

```
L49             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIZATION+PFT,OLD,NEW,NT
                /CT
L50             QUE  SPE=ON  ABB=ON  PLU=ON  ACETYLATION+PFT,OLD,NEW,NT/C
                T
L51             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLATION+PFT,OLD,NEW,NT/CT
L52             QUE  SPE=ON  ABB=ON  PLU=ON  DEACETYLATION+PFT,OLD,NEW,NT
                /CT
L53             QUE  SPE=ON  ABB=ON  PLU=ON  DEACYLATION+PFT,OLD,NEW,NT/C
                T
L55        5405 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L18
L56         159 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L55 (L)(PREP+NT)/RL
L57        4264 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L15
L58         162 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L57 (L)(RACT+NT)/RL
L59          69 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L56 AND L58
L60          26 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L22
L61           3 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L26
L62          40 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L30
L63           9 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L59 AND (L60 OR L61
                OR L62)
L64          13 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L59 AND L49
L66           1 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L59 AND L9
L67           1 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L59 AND (L48(L)L44)
L68          19 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L63 OR L64 OR (L66 OR
                L67)
L69          19 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L68 AND (L41 OR L42
                OR L43 OR L44 OR L45 OR L46 OR L47 OR L48 OR L49 OR L50 OR L51
                OR L52 OR L53)
L70          19 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L68 OR L69
L71           2 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L70 AND (L31 OR L32
                OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L72          17 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L70 NOT L71


=> d que nos l102
L6              STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L16             STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L102          0 SEA FILE=CHEMINFORMRX SPE=ON  ABB=ON  PLU=ON  L18


=> d que l100
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
```

```
L54             QUE  SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHET
                IC? OR PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD?
                OR MAKE OR MAKING OR MADE OR PROCESS? OR GIVE OR GIVING O
                R GAVE OR FORMING OR FORM OR FORMATION OR FORMS OR FORMED
L84           1 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  LOVASTATIN/CN
L85          97 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  99623/DCSE
L86        1315 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  R16653/DCN OR R19716/DCN
                OR L85/DCR OR L84/DCR
L87          36 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L86(T)(S OR RCT)/DCN,DCR

L88           1 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN/CN
L89           5 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  107036/DCSE
L90        1291 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L88/DCR OR L89/DCR OR
                R16884/DCN
L91          87 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L90 (T) (P OR PRD)/DCN,DC
                R
L92          21 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L87 AND L91
L93           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L92 AND L46
L94           4 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L93 AND (L47 OR DEACYL?/B
                IX,BIEX,ABEX,TT OR ACETYLAT?/BIX,BIEX,ABEX,TT OR DEACETYLAT?/BI
                X,BIEX,ABEX,TT)
L95           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  (L93 OR L94)
L96           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L95 AND (L41 OR L42 OR
                L43 OR L44 OR L45 OR L46 OR L47)
L97           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L95 AND L54
L98           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  (L95 OR L96 OR L97)
L99           1 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L98 AND (L31 OR L32 OR
                L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L100          7 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L98 NOT L99


=> d que nos l116
L6              STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L13             STR
L15         199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16             STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L103       3947 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L18
L104            QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN+PFT,OLD,NEW,NT/C
                T (P)CS/CT
L105       3692 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L15
```

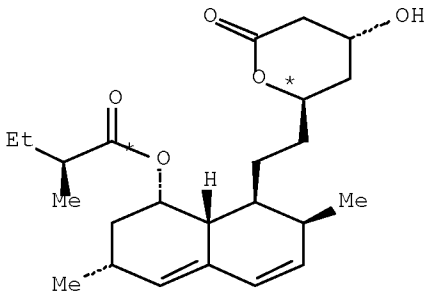
```
L106       3947 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L103 OR L104
L107            QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN+PFT,OLD,NEW,NT/CT
                 (P) CH/CT
L108       3733 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L105 OR L107
L109       1133 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L106 AND L108
L110          2 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L109 AND L104
L111          2 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L109 AND L46
L112          4 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  (L110 OR L111)
L113          4 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L112 AND (L41 OR L42
                OR L43 OR L44 OR L45 OR L46 OR L47)
L114          4 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L112 OR L113
L115          0 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L114 AND (L31 OR L32
                OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L116          4 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L114 NOT L115


=> d que nos l132
L6              STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L13             STR
L15         199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16             STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L20             STR
L22          18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24             STR
L26           5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28             STR
L30         800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L54             QUE  SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHET
                IC? OR PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD?
                OR MAKE OR MAKING OR MADE OR PROCESS? OR GIVE OR GIVING O
                R GAVE OR FORMING OR FORM OR FORMATION OR FORMS OR FORMED
L73          823 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 OR L26 OR L30
L117       15476 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L18
L118         381 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L54(5A)(L42 OR L43)
L119        9261 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L15
L122        4661 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L117 AND L119
L123           0 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L73
L124          65 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L122 AND (L123 OR
                L118)
L125          15 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L124 AND (L46 OR
```

```
                LACTONE)
L126          0 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L125 AND (L47 OR
                ACETYLAT? OR DEACYL? OR DEACETYL?)
L127         15 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  (L125 OR L126)
L128         15 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L127 AND (L41 OR L42
                OR L43 OR L44 OR L45 OR L46 OR L47)
L129         15 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  (L127 OR L128)
L130          2 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L129 AND L46
L131          0 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L130 AND (L31 OR L32
                OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L132          2 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L130 NOT L131


=> d his l143

     (FILE 'BIOSIS, CABA, BIOTECHNO, DRUGU, VETU' ENTERED AT 10:53:32 ON 23
     JUN 2009)
L143          1 S L141 NOT L142

=> d que nos l143
L6                STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L13               STR
L15         199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16               STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L20               STR
L22          18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24               STR
L26           5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28               STR
L30         800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L31               QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32               QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33               QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34               QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35               QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36               QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37               QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38               QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39               QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40               QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                  PA
L41               QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42               QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43               QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44               QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45               QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46               QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47               QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L54               QUE  SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHET
                  IC? OR PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD?
                  OR MAKE OR MAKING OR MADE OR PROCESS? OR GIVE OR GIVING O
                  R GAVE OR FORMING OR FORM OR FORMATION OR FORMS OR FORMED
L73          823 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 OR L26 OR L30
L133       10730 SEA L18
L134        5907 SEA L15
L135        1252 SEA L133 AND L134
L136           0 SEA L73
L137         100 SEA (L54 (5A) L42) (8A) L41
```

```
L138         45 SEA L135 AND ((L136 OR L137))
L139          1 SEA L138 AND L46
L140          1 SEA L139 AND (L41 OR L42 OR L43 OR L44 OR L45 OR L46 OR L47)
L141          1 SEA L139 OR L140
L142          0 SEA L141 AND (L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR
                L38 OR L39 OR L40)
L143          1 SEA L141 NOT L142


=> d his l149

     (FILE 'PASCAL, JAPIO, LIFESCI, BIOENG, BIOTECHDS, DRUGB, VETB, SCISEARCH,
     CONFSCI, DISSABS, RDISCLOSURE' ENTERED AT 10:57:03 ON 23 JUN 2009)
L149          2 S L147 NOT L148

     FILE 'STNGUIDE' ENTERED AT 11:01:19 ON 23 JUN 2009

=> d que nos l149
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L54             QUE  SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHET
                IC? OR PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD?
                OR MAKE OR MAKING OR MADE OR PROCESS? OR GIVE OR GIVING O
                R GAVE OR FORMING OR FORM OR FORMATION OR FORMS OR FORMED
L144         77 SEA (L54 (5A) L42) (8A) L41
L145          3 SEA L144 AND L46
L146          3 SEA L145 AND (L41 OR L42 OR L43 OR L44 OR L45 OR L46 OR L47)
L147          3 SEA (L145 OR L146)
L148          1 SEA L147 AND (L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR
                L38 OR L39 OR L40)
L149          2 SEA L147 NOT L148


=> dup rem l82 l72 l100 l102 l116 l132 l143 l149
L102 HAS NO ANSWERS
DUPLICATE IS NOT AVAILABLE IN 'CHEMINFORMRX, RDISCLOSURE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'CASREACT' ENTERED AT 11:04:41 ON 23 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'HCAPLUS' ENTERED AT 11:04:41 ON 23 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
```

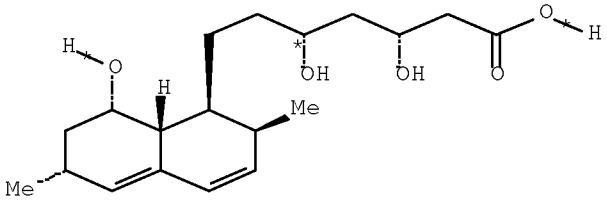
```
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIX' ENTERED AT 11:04:41 ON 23 JUN 2009
COPYRIGHT (C) 2009 THOMSON REUTERS

FILE 'MEDLINE' ENTERED AT 11:04:41 ON 23 JUN 2009

FILE 'EMBASE' ENTERED AT 11:04:41 ON 23 JUN 2009
Copyright (c) 2009 Elsevier B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 11:04:41 ON 23 JUN 2009
Copyright (c) 2009 The Thomson Corporation

FILE 'JAPIO' ENTERED AT 11:04:41 ON 23 JUN 2009
COPYRIGHT (C) 2009 Japanese Patent Office (JPO)- JAPIO

FILE 'BIOTECHDS' ENTERED AT 11:04:41 ON 23 JUN 2009
COPYRIGHT (C) 2009 THOMSON REUTERS
PROCESSING COMPLETED FOR L82
PROCESSING COMPLETED FOR L72
PROCESSING COMPLETED FOR L100
PROCESSING COMPLETED FOR L102
PROCESSING COMPLETED FOR L116
PROCESSING COMPLETED FOR L132
PROCESSING COMPLETED FOR L143
PROCESSING COMPLETED FOR L149
L150         29 DUP REM L82 L72 L100 L102 L116 L132 L143 L149 (9 DUPLICATES
REMOVED)
                ANSWERS '1-5' FROM FILE CASREACT
                ANSWERS '6-17' FROM FILE HCAPLUS
                ANSWERS '18-20' FROM FILE WPIX
                ANSWERS '21-24' FROM FILE MEDLINE
                ANSWERS '25-26' FROM FILE EMBASE
                ANSWER '27' FROM FILE BIOSIS
                ANSWER '28' FROM FILE JAPIO
                ANSWER '29' FROM FILE BIOTECHDS


=> file stnguide
FILE 'STNGUIDE' ENTERED AT 11:05:08 ON 23 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jun 19, 2009 (20090619/UP).
```

```
=> d ibib abs hit
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE,
BIOSIS, JAPIO, BIOTECHDS' - CONTINUE? (Y)/N:y



L150 ANSWER 1 OF 29  CASREACT  COPYRIGHT 2009 ACS on STN DUPLICATE 1
ACCESSION NUMBER:        150:191324  CASREACT  Full-text
TITLE:                   Process for preparation of simvastatin
INVENTOR(S):             Singh, Harnam; Dubey, Shailendra Kumar; Gupta, Nitin;
                         Dubey, Sushil Kumar
PATENT ASSIGNEE(S):      Jubilant Organosys Limited, India
SOURCE:                  PCT Int. Appl., 17pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2009013764      A2   20090129       WO 2008-IN467    20080724
     WO 2009013764      A3   20090319
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
             CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
             FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
             KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
             ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
             PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,
             TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
             IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK,
             TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
             TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
     IN 2007DE01554     A    20090424       IN 2007-DE1554   20070724
PRIORITY APPLN. INFO.:                     IN 2007-DE1554   20070724
AB    The present invention pertains to an improved process for producing
      simvastatin, an HMG-CoA reductase inhibitor.  For example, (+)-mevinolin was
      treated with KOH in isopropanol for hydrolysis to afford (3R,5R)-7-
      [(1S,2S,6R,8S,8aR)-1,2,6,7,8,8a-hexahydro-2,6-dimethyl-8-hydroxy- 1-naphthyl]-
      3,5-dihydroxyheptanoic acid, which was then treated with p-toluene sulfonic
      acid in dichloromethane to afford lovastatin diol lactone.  The intermediate
      obtained above was reacted with tert-butyldimethylchlorosilane to protect the
      hydroxyl group on lactone ring, reacted with 2,2-di-Me butyryl chloride, then
      treated with butylated hydroxyanisole, p-toluene sulfonic acid in DMF to give
      simvastatin as the final product.  Advantageously, the new process is an
      industrially feasible, high yielding and cost effective process for the
      preparation of simvastatin, which requires less reaction time with reduced
      formation of byproducts.



RX(1) OF 15      A  ===>  B...
```



A

(1)



B
YIELD 95%

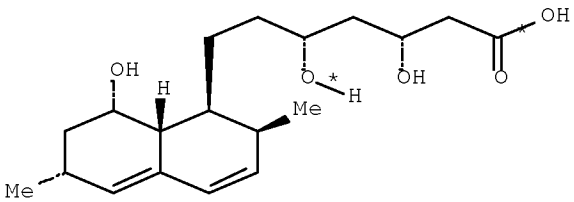
RX(1) RCT A 75330-75-5

STAGE(1)
RGT C 1310-58-3 KOH
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-, 128-37-0
2,6-Di-t-butylcresol
SOL 67-63-0 Me2CHOH
CON SUBSTAGE(1) room temperature -> 70 deg C
SUBSTAGE(3) 9 - 12 hours
SUBSTAGE(4) 70 - 75 deg C
SUBSTAGE(5) 75 deg C -> 50 deg C

STAGE(2)
RGT D 7647-01-0 HCl
SOL 7732-18-5 Water
CON SUBSTAGE(1) 0 - 5 deg C
SUBSTAGE(2) pH 1.5 - 2

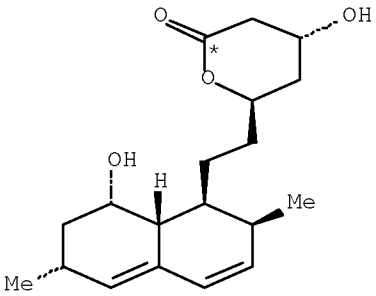
PRO B 132748-10-8

RX(2) OF 15 ...B ===> I...



B

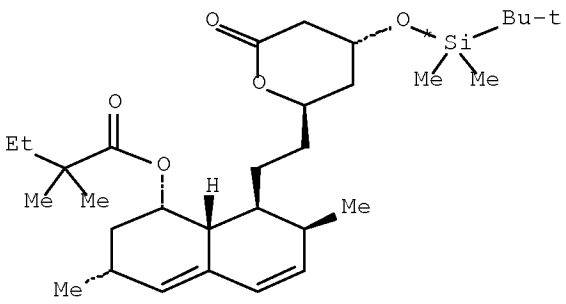
(2)



I
YIELD 90%

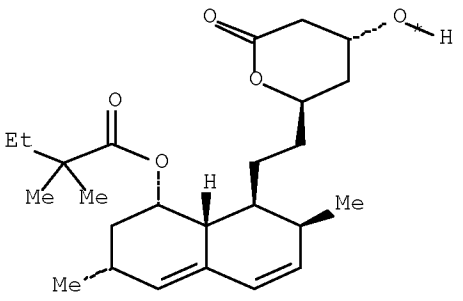
RX(2) RCT B 132748-10-8
PRO I 79952-42-4
CAT 104-15-4 TsOH
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 5 deg C
SUBSTAGE(2) 0 - 5 deg C
SUBSTAGE(3) 2 hours, 0 - 15 deg C

RX(5) OF 15 ...P ===> S



P

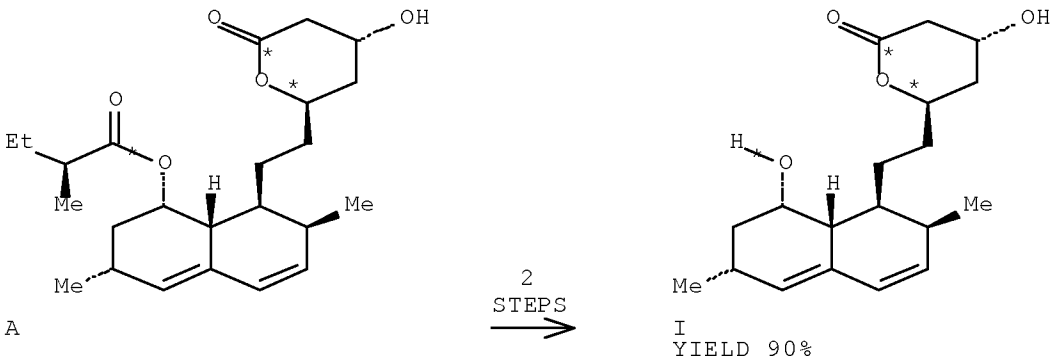
(5)



S
YIELD 96%

RX(5) RCT P 79902-59-3
RGT J 104-15-4 TsOH
PRO S 79902-63-9
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-
SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature -> 15 deg C
SUBSTAGE(2) 14 - 20 hours, 15 - 20 deg C

RX(6) OF 15 COMPOSED OF RX(1), RX(2)
RX(6) A ===> I



A

2
STEPS

I
YIELD 90%

RX(1) RCT A 75330-75-5

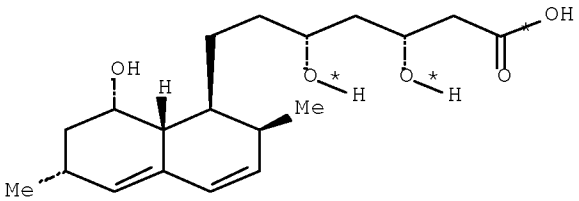
STAGE(1)
RGT C 1310-58-3 KOH
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-, 128-37-0
2,6-Di-t-butylcresol
SOL 67-63-0 Me2CHOH
CON SUBSTAGE(1) room temperature -> 70 deg C
SUBSTAGE(3) 9 - 12 hours
SUBSTAGE(4) 70 - 75 deg C
SUBSTAGE(5) 75 deg C -> 50 deg C

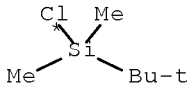
STAGE(2)
RGT D 7647-01-0 HCl
SOL 7732-18-5 Water
CON SUBSTAGE(1) 0 - 5 deg C
SUBSTAGE(2) pH 1.5 - 2

PRO B 132748-10-8

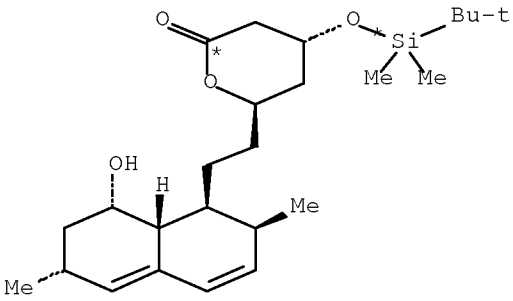
RX(2) RCT B 132748-10-8
PRO I 79952-42-4
CAT 104-15-4 TsOH
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 5 deg C
SUBSTAGE(2) 0 - 5 deg C
SUBSTAGE(3) 2 hours, 0 - 15 deg C

RX(7) OF 15 COMPOSED OF RX(2), RX(3)
RX(7) B + L ===> M





2 STEPS



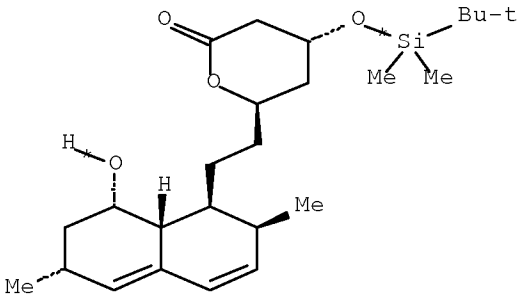
M
YIELD 90%

RX(2) RCT B 132748-10-8
PRO I 79952-42-4
CAT 104-15-4 TsOH
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 5 deg C
SUBSTAGE(2) 0 - 5 deg C

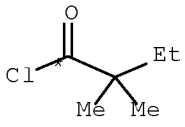
SUBSTAGE(3) 2 hours, 0 - 15 deg C

RX(3) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2
CON 4 - 6 hours, 35 - 40 deg C

RX(9) OF 15 COMPOSED OF RX(4), RX(5)
RX(9) M + O ===> S

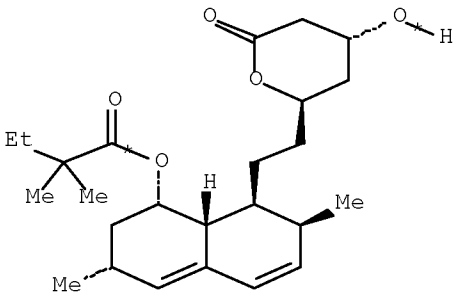


M



O

2 STEPS



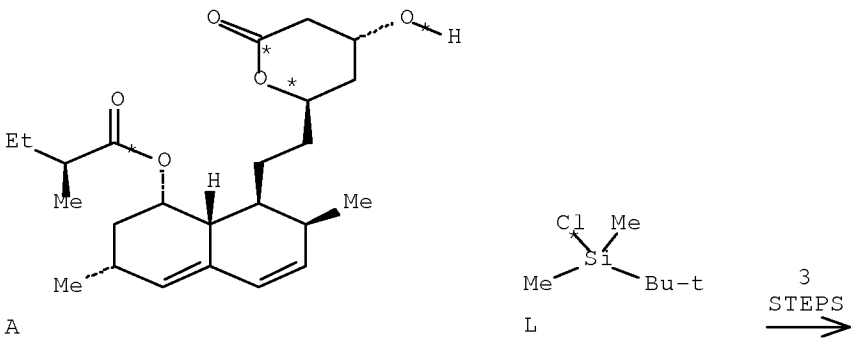
S
YIELD 96%

RX(4) RCT M 79902-31-1, O 5856-77-9
RGT Q 121-44-8 Et3N
PRO P 79902-59-3
SOL 108-88-3 PhMe
CON 19 - 24 hours, room temperature -> 110 deg C

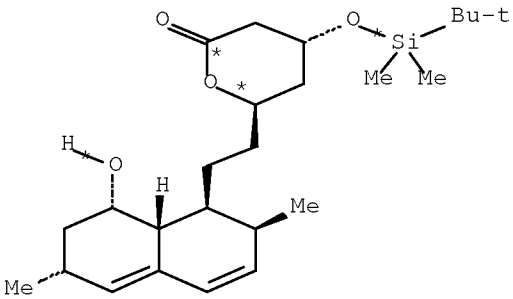
RX(5) RCT P 79902-59-3
RGT J 104-15-4 TsOH
PRO S 79902-63-9
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-
SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature -> 15 deg C

SUBSTAGE(2) 14 - 20 hours, 15 - 20 deg C

RX(10) OF 15 COMPOSED OF RX(1), RX(2), RX(3)
RX(10) A + L ===> M



A L



M
YIELD 90%

RX(1) RCT A 75330-75-5

STAGE(1)
RGT C 1310-58-3 KOH
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-, 128-37-0
2,6-Di-t-butylcresol
SOL 67-63-0 Me2CHOH
CON SUBSTAGE(1) room temperature -> 70 deg C
SUBSTAGE(3) 9 - 12 hours
SUBSTAGE(4) 70 - 75 deg C
SUBSTAGE(5) 75 deg C -> 50 deg C

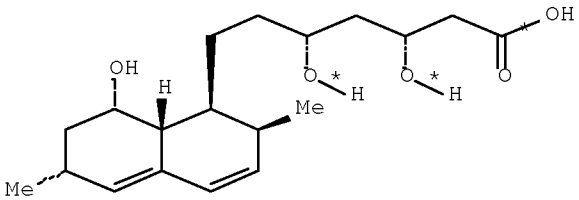
STAGE(2)
RGT D 7647-01-0 HCl
SOL 7732-18-5 Water
CON SUBSTAGE(1) 0 - 5 deg C
SUBSTAGE(2) pH 1.5 - 2

PRO B 132748-10-8

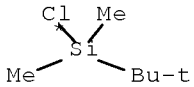
RX(2) RCT B 132748-10-8
PRO I 79952-42-4
CAT 104-15-4 TsOH
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 5 deg C
SUBSTAGE(2) 0 - 5 deg C
SUBSTAGE(3) 2 hours, 0 - 15 deg C

RX(3) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2
CON 4 - 6 hours, 35 - 40 deg C

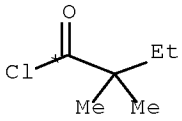
RX(11) OF 15 COMPOSED OF RX(2), RX(3), RX(4)
RX(11) B + L + O ===> P



B

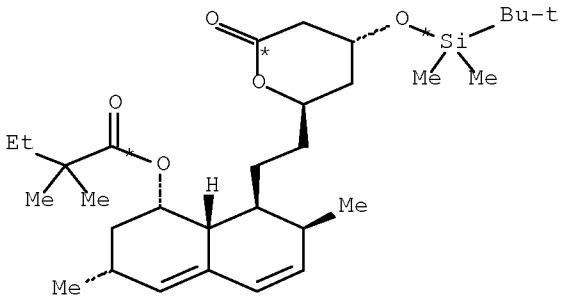


L



O

3
STEPS



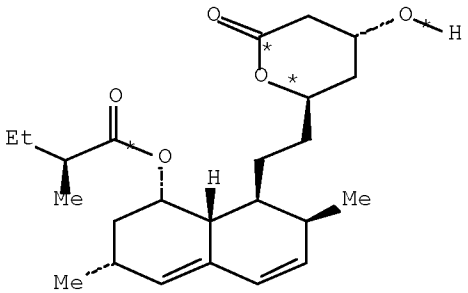
P
YIELD 92%

RX(2) RCT B 132748-10-8
PRO I 79952-42-4
CAT 104-15-4 TsOH
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 5 deg C
SUBSTAGE(2) 0 - 5 deg C
SUBSTAGE(3) 2 hours, 0 - 15 deg C

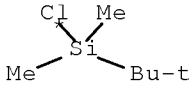
RX(3) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2
CON 4 - 6 hours, 35 - 40 deg C

RX(4) RCT M 79902-31-1, O 5856-77-9
RGT Q 121-44-8 Et3N
PRO P 79902-59-3
SOL 108-88-3 PhMe
CON 19 - 24 hours, room temperature -> 110 deg C

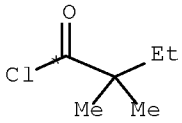
RX(12) OF 15 COMPOSED OF RX(1), RX(2), RX(3), RX(4)
RX(12) A + L + O ===> P



A

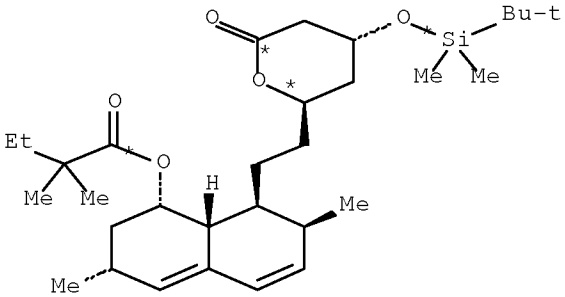


L



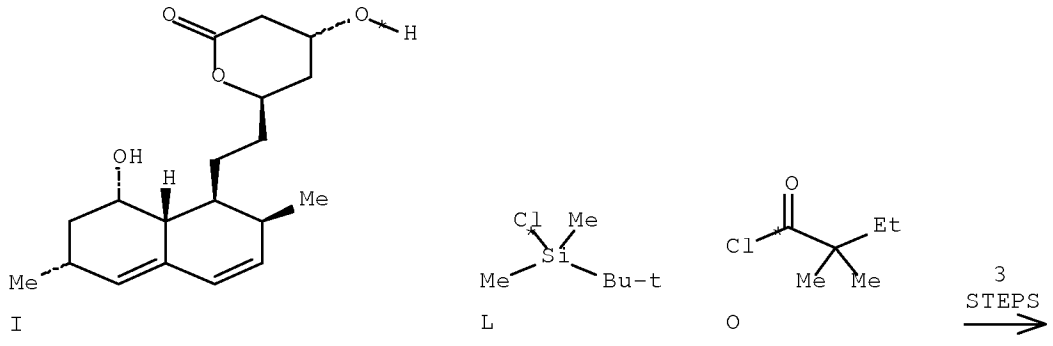
O

4
STEPS

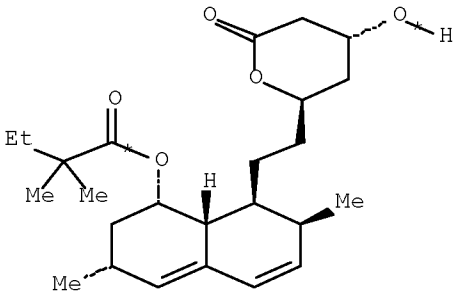


P
YIELD 92%

```
RX(1)      RCT  A 75330-75-5

             STAGE(1)
                RGT  C 1310-58-3 KOH
                CAT  25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-, 128-37-0
                     2,6-Di-t-butylcresol
                SOL  67-63-0 Me2CHOH
                CON  SUBSTAGE(1) room temperature -> 70 deg C
                     SUBSTAGE(3) 9 - 12 hours
                     SUBSTAGE(4) 70 - 75 deg C
                     SUBSTAGE(5) 75 deg C -> 50 deg C

             STAGE(2)
                RGT  D 7647-01-0 HCl
                SOL  7732-18-5 Water
                CON  SUBSTAGE(1) 0 - 5 deg C
                     SUBSTAGE(2) pH 1.5 - 2

           PRO  B 132748-10-8

RX(2)      RCT  B 132748-10-8
           PRO  I 79952-42-4
           CAT  104-15-4 TsOH
           SOL  75-09-2 CH2Cl2
           CON  SUBSTAGE(1) room temperature -> 5 deg C
                SUBSTAGE(2) 0 - 5 deg C
                SUBSTAGE(3) 2 hours, 0 - 15 deg C

RX(3)      RCT  I 79952-42-4, L 18162-48-6
           RGT  N 288-32-4 1H-Imidazole
           PRO  M 79902-31-1
           SOL  75-09-2 CH2Cl2
           CON  4 - 6 hours, 35 - 40 deg C

RX(4)      RCT  M 79902-31-1, O 5856-77-9
           RGT  Q 121-44-8 Et3N
           PRO  P 79902-59-3
           SOL  108-88-3 PhMe
           CON  19 - 24 hours, room temperature -> 110 deg C


RX(13) OF 15 COMPOSED OF RX(3), RX(4), RX(5)
RX(13)    I  +  L  +  O  ===>  S
```



I L O



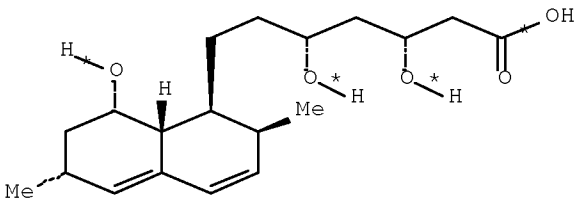
S
YIELD 96%

RX(3) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2
CON 4 - 6 hours, 35 - 40 deg C

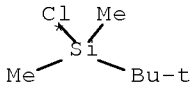
RX(4) RCT M 79902-31-1, O 5856-77-9
RGT Q 121-44-8 Et3N
PRO P 79902-59-3
SOL 108-88-3 PhMe
CON 19 - 24 hours, room temperature -> 110 deg C

RX(5) RCT P 79902-59-3
RGT J 104-15-4 TsOH
PRO S 79902-63-9
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-
SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature -> 15 deg C
SUBSTAGE(2) 14 - 20 hours, 15 - 20 deg C

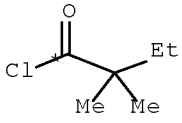
RX(14) OF 15 COMPOSED OF RX(2), RX(3), RX(4), RX(5)
RX(14) B + L + O ===> S



B

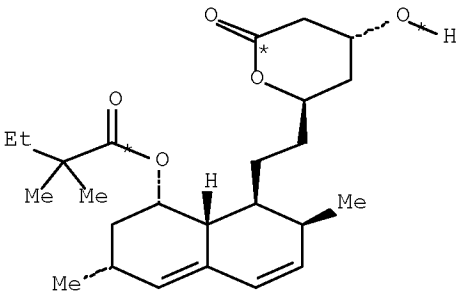


L



O

4
STEPS



S
YIELD 96%

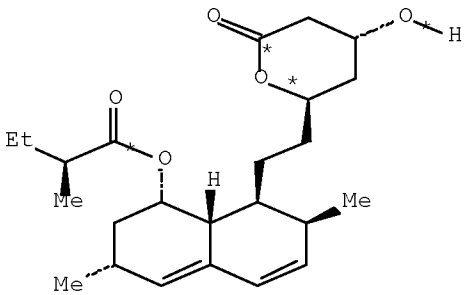
RX(2) RCT B 132748-10-8
PRO I 79952-42-4
CAT 104-15-4 TsOH
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 5 deg C
SUBSTAGE(2) 0 - 5 deg C
SUBSTAGE(3) 2 hours, 0 - 15 deg C

RX(3) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2
CON 4 - 6 hours, 35 - 40 deg C

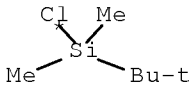
RX(4) RCT M 79902-31-1, O 5856-77-9
RGT Q 121-44-8 Et3N
PRO P 79902-59-3
SOL 108-88-3 PhMe
CON 19 - 24 hours, room temperature -> 110 deg C

RX(5) RCT P 79902-59-3
RGT J 104-15-4 TsOH
PRO S 79902-63-9
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-
SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature -> 15 deg C
SUBSTAGE(2) 14 - 20 hours, 15 - 20 deg C

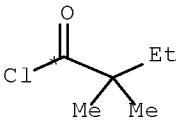
RX(15) OF 15 COMPOSED OF RX(1), RX(2), RX(3), RX(4), RX(5)
RX(15) A + L + O ===> S



A

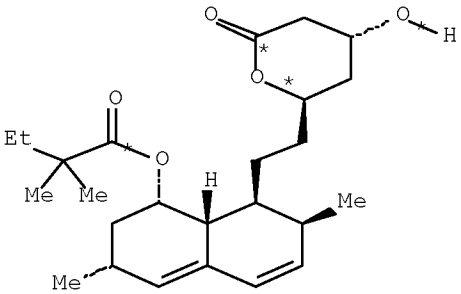


L



O

5
STEPS



S
YIELD 96%

RX(1) RCT A 75330-75-5

STAGE(1)
RGT C 1310-58-3 KOH
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-, 128-37-0
2,6-Di-t-butylcresol
SOL 67-63-0 Me2CHOH
CON SUBSTAGE(1) room temperature -> 70 deg C
SUBSTAGE(3) 9 - 12 hours
SUBSTAGE(4) 70 - 75 deg C
SUBSTAGE(5) 75 deg C -> 50 deg C

STAGE(2)
RGT D 7647-01-0 HCl
SOL 7732-18-5 Water
CON SUBSTAGE(1) 0 - 5 deg C
SUBSTAGE(2) pH 1.5 - 2

PRO B 132748-10-8

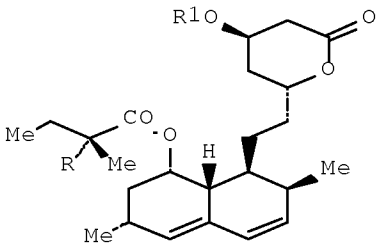
RX(2) RCT B 132748-10-8
PRO I 79952-42-4
CAT 104-15-4 TsOH
SOL 75-09-2 CH2Cl2

```
          CON  SUBSTAGE(1) room temperature -> 5 deg C
               SUBSTAGE(2) 0 - 5 deg C
               SUBSTAGE(3) 2 hours, 0 - 15 deg C

RX(3)     RCT  I 79952-42-4, L 18162-48-6
          RGT  N 288-32-4 1H-Imidazole
          PRO  M 79902-31-1
          SOL  75-09-2 CH2Cl2
          CON  4 - 6 hours, 35 - 40 deg C

RX(4)     RCT  M 79902-31-1, O 5856-77-9
          RGT  Q 121-44-8 Et3N
          PRO  P 79902-59-3
          SOL  108-88-3 PhMe
          CON  19 - 24 hours, room temperature -> 110 deg C

RX(5)     RCT  P 79902-59-3
          RGT  J 104-15-4 TsOH
          PRO  S 79902-63-9
          CAT  25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-
          SOL  68-12-2 DMF
          CON  SUBSTAGE(1) room temperature -> 15 deg C
               SUBSTAGE(2) 14 - 20 hours, 15 - 20 deg C


=> d ibib abs hit 2-5
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE,
BIOSIS, JAPIO, BIOTECHDS' - CONTINUE? (Y)/N:y




L150 ANSWER 2 OF 29  CASREACT  COPYRIGHT 2009 ACS on STN DUPLICATE 2
ACCESSION NUMBER:        147:300893  CASREACT  Full-text
TITLE:                   Process for preparing highly pure simvastatin
INVENTOR(S):             Upadhyay, G. Umesh; Shah, Niraj Kumar Shyamial; Kumar,
                         Rajiv; Dwivedi, Shri Prakash Dhar
PATENT ASSIGNEE(S):      Cadila Healthcare Limited, India
SOURCE:                  PCT Int. Appl., 12pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2007096753      A2   20070830       WO 2007-IB429    20070221
     WO 2007096753      A3   20071115
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
             KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
             MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
             RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
```

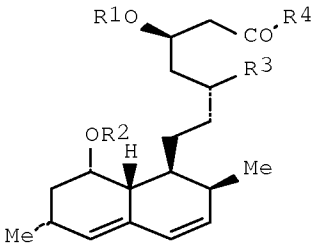
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.: IN 2006-MU244 20060221

GI



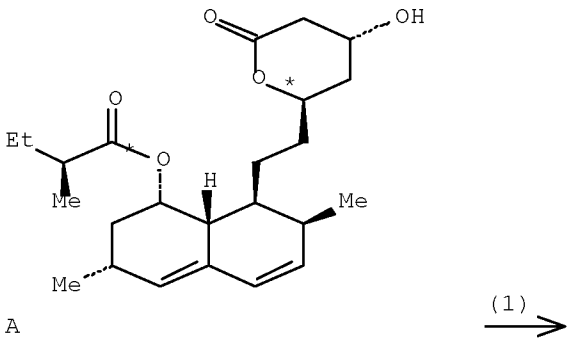
I



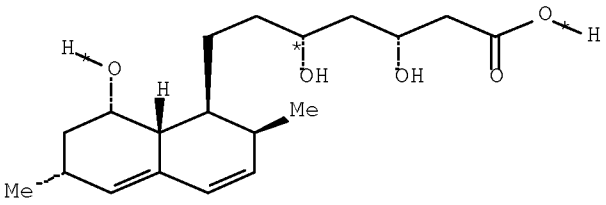
II

AB A process was disclosed for the preparation of the pharmaceutically useful simvastatin I (R = Me, R1 = H) via the prepn of silylated simvastatin I (R = Me, R1 = SiMe2CMe3). The process comprised hydrolyzing lovastatin I (R = R1 = H) to give triol lactone II (R1 = R2 = H, R3 = R4 = OH), lactonization of the triol lactone to form diol lactone II (R1 = R2 = H, R3R4 = O), regioselective silylation of the diol lactone with ClSiMe2CMe3 to give mono-silylated lactone II (R1 = SiMe2CMe3, R2 = H, R3R4 = O), and finally, acylation of the mono-silylated lactone with MeCH2CMe2COCl to give the target silylated simvastatin. The silylated simvastatin was further converted to simvastatin with 99.7% purity and 95% yield for the final desilylation step.

RX(1) OF 15 A ===> B...



A



B
YIELD 93%

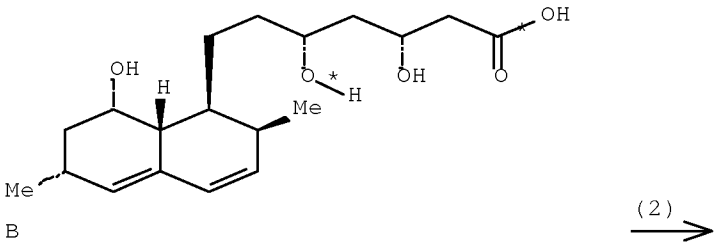
RX(1) RCT A 75330-75-5

STAGE(1)
RGT C 1310-73-2 NaOH
SOL 67-56-1 MeOH
CON SUBSTAGE(1) 40 deg C
SUBSTAGE(2) 15 hours, 65 - 75 deg C
SUBSTAGE(3) 75 deg C -> 35 deg C

STAGE(2)
RGT D 7647-01-0 HCl
SOL 7732-18-5 Water
CON SUBSTAGE(1) pH 7.5 - 8
SUBSTAGE(2) cooled, pH 1.5 - 2

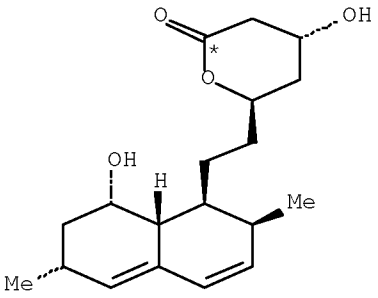
PRO B 132748-10-8

RX(2) OF 15 ...B ===> G...



B

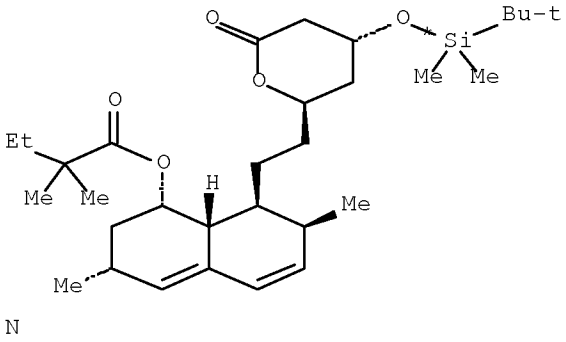
(2) →



G
YIELD 90%

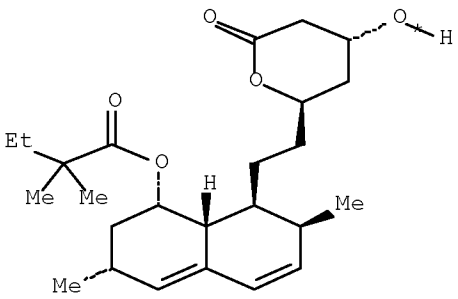
RX(2) RCT B 132748-10-8
PRO G 79952-42-4
SOL 7732-18-5 Water, 108-88-3 PhMe
CON SUBSTAGE(1) room temperature -> 110 deg C
SUBSTAGE(2) 2 hours, reflux

RX(5) OF 15 ...N ===> R



N

(5)



R
YIELD 95%

RX(5) RCT N 79902-59-3

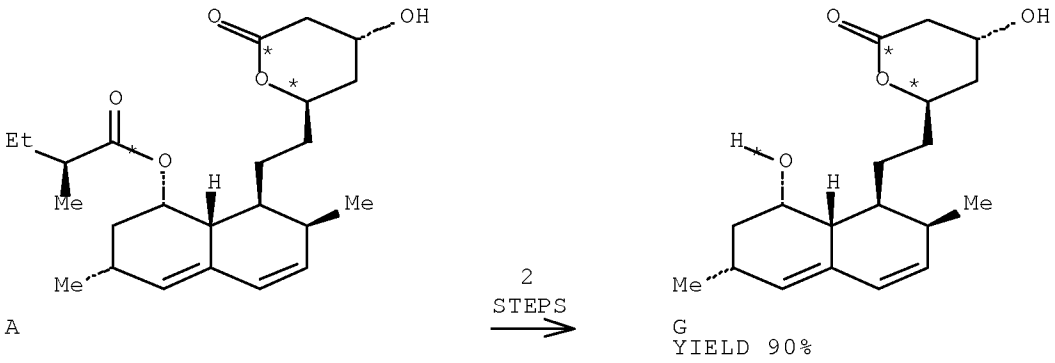
STAGE(1)
SOL 109-99-9 THF
CON 15 minutes, 25 - 35 deg C

STAGE(2)
RGT S 64-19-7 AcOH
SOL 7732-18-5 Water
CON 35 deg C -> 20 deg C

STAGE(3)
RGT T 429-41-4 Bu4N.F
SOL 109-99-9 THF
CON 30 - 35 hours, 18 - 22 deg C

PRO R 79902-63-9

RX(6) OF 15 COMPOSED OF RX(1), RX(2)
RX(6) A ===> G



A

G
YIELD 90%

RX(1) RCT A 75330-75-5

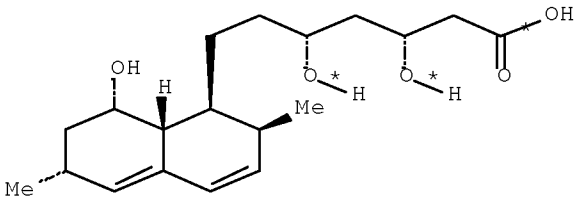
STAGE(1)
RGT C 1310-73-2 NaOH
SOL 67-56-1 MeOH
CON SUBSTAGE(1) 40 deg C
SUBSTAGE(2) 15 hours, 65 - 75 deg C
SUBSTAGE(3) 75 deg C -> 35 deg C

STAGE(2)
RGT D 7647-01-0 HCl
SOL 7732-18-5 Water
CON SUBSTAGE(1) pH 7.5 - 8
SUBSTAGE(2) cooled, pH 1.5 - 2

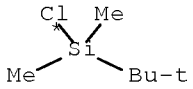
PRO B 132748-10-8

RX(2) RCT B 132748-10-8
PRO G 79952-42-4
SOL 7732-18-5 Water, 108-88-3 PhMe
CON SUBSTAGE(1) room temperature -> 110 deg C
SUBSTAGE(2) 2 hours, reflux

RX(7) OF 15 COMPOSED OF RX(2), RX(3)
RX(7) B + I ===> J

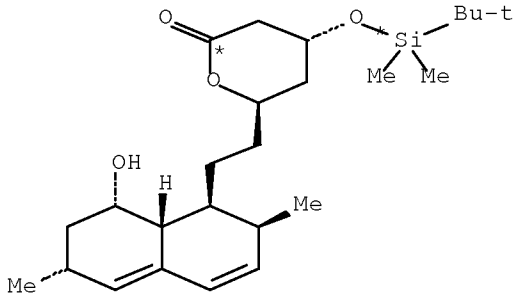


B



I

2 STEPS



J
YIELD 1%

RX(2) RCT B 132748-10-8
PRO G 79952-42-4
SOL 7732-18-5 Water, 108-88-3 PhMe
CON SUBSTAGE(1) room temperature -> 110 deg C
SUBSTAGE(2) 2 hours, reflux

RX(3)

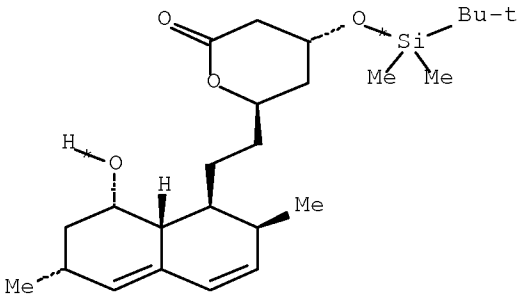
STAGE(1)
RGT K 288-32-4 1H-Imidazole
SOL 68-12-2 DMF
CON 30 deg C -> 20 deg C

STAGE(2)
RCT I 18162-48-6
CON 15 - 20 deg C

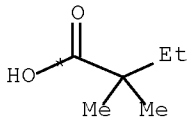
STAGE(3)
RCT G 79952-42-4
SOL 68-12-2 DMF
CON 3 hours, 15 - 20 deg C

PRO J 79902-31-1

RX(9) OF 15 COMPOSED OF RX(4), RX(5)
RX(9) J + M ===> R

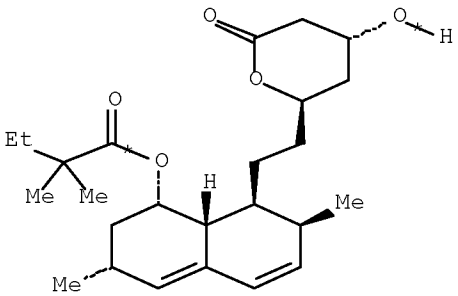


J



M

2 STEPS →



R
YIELD 95%

RX(4) RCT J 79902-31-1

STAGE(1)
RGT O 110-86-1 Pyridine
CAT 1122-58-3 4-DMAP
SOL 110-82-7 Cyclohexane
CON 15 minutes, 20 - 25 deg C

STAGE(2)
RCT M 595-37-9
SOL 110-82-7 Cyclohexane
CON SUBSTAGE(1) 25 deg C -> 90 deg C

SUBSTAGE(2) 36 hours, 90 deg C

PRO N 79902-59-3

RX(5) RCT N 79902-59-3

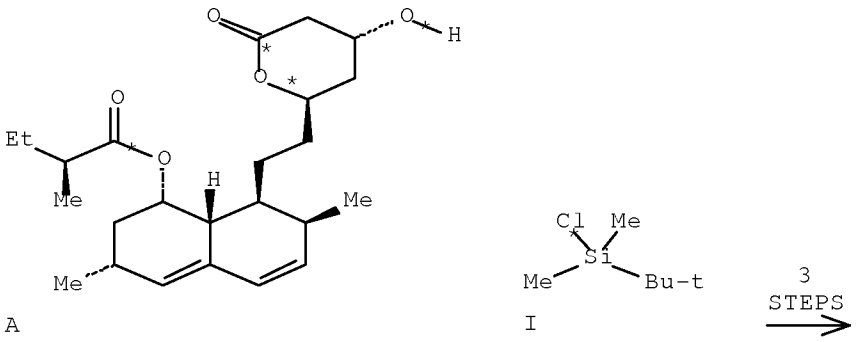
STAGE(1)
SOL 109-99-9 THF
CON 15 minutes, 25 - 35 deg C

STAGE(2)
RGT S 64-19-7 AcOH
SOL 7732-18-5 Water
CON 35 deg C -> 20 deg C

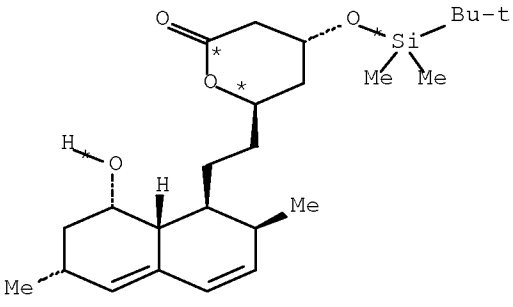
STAGE(3)
RGT T 429-41-4 Bu4N.F
SOL 109-99-9 THF
CON 30 - 35 hours, 18 - 22 deg C

PRO R 79902-63-9

RX(10) OF 15 COMPOSED OF RX(1), RX(2), RX(3)
RX(10) A + I ===> J



A I



J
YIELD 1%

RX(1) RCT A 75330-75-5

STAGE(1)
RGT C 1310-73-2 NaOH
SOL 67-56-1 MeOH
CON SUBSTAGE(1) 40 deg C
SUBSTAGE(2) 15 hours, 65 - 75 deg C
SUBSTAGE(3) 75 deg C -> 35 deg C

STAGE(2)
RGT D 7647-01-0 HCl
SOL 7732-18-5 Water
CON SUBSTAGE(1) pH 7.5 - 8
SUBSTAGE(2) cooled, pH 1.5 - 2

PRO B 132748-10-8

RX(2) RCT B 132748-10-8
PRO G 79952-42-4
SOL 7732-18-5 Water, 108-88-3 PhMe
CON SUBSTAGE(1) room temperature -> 110 deg C
SUBSTAGE(2) 2 hours, reflux

RX(3)

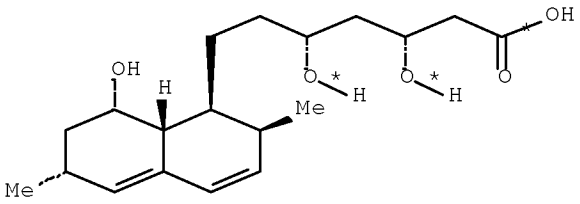
STAGE(1)
RGT K 288-32-4 1H-Imidazole
SOL 68-12-2 DMF
CON 30 deg C -> 20 deg C

STAGE(2)
RCT I 18162-48-6
CON 15 - 20 deg C

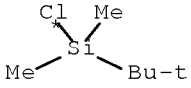
STAGE(3)
RCT G 79952-42-4
SOL 68-12-2 DMF
CON 3 hours, 15 - 20 deg C

PRO J 79902-31-1

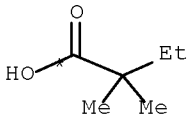
RX(11) OF 15 COMPOSED OF RX(2), RX(3), RX(4)
RX(11) B + I + M ===> N



B

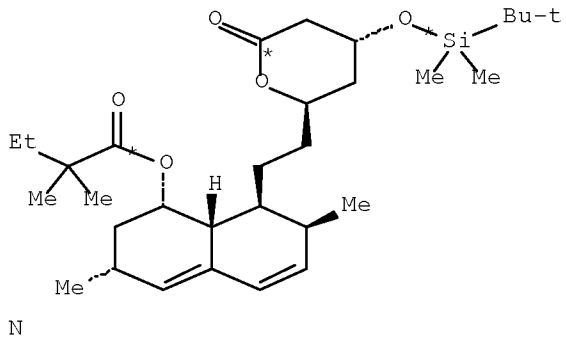


I



M

3
STEPS



N

RX(2) RCT B 132748-10-8
PRO G 79952-42-4
SOL 7732-18-5 Water, 108-88-3 PhMe
CON SUBSTAGE(1) room temperature -> 110 deg C
SUBSTAGE(2) 2 hours, reflux

RX(3)

STAGE(1)
RGT K 288-32-4 1H-Imidazole
SOL 68-12-2 DMF
CON 30 deg C -> 20 deg C

STAGE(2)
RCT I 18162-48-6
CON 15 - 20 deg C

STAGE(3)
RCT G 79952-42-4
SOL 68-12-2 DMF
CON 3 hours, 15 - 20 deg C

PRO J 79902-31-1

RX(4) RCT J 79902-31-1

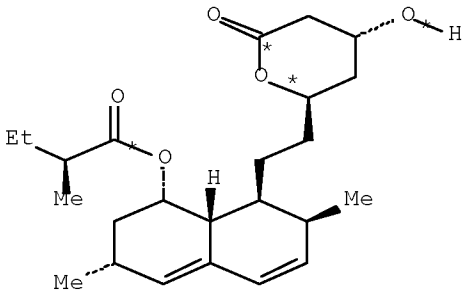
STAGE(1)
RGT O 110-86-1 Pyridine
CAT 1122-58-3 4-DMAP
SOL 110-82-7 Cyclohexane
CON 15 minutes, 20 - 25 deg C

STAGE(2)

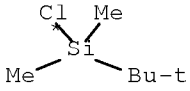
RCT M 595-37-9
SOL 110-82-7 Cyclohexane
CON SUBSTAGE(1) 25 deg C -> 90 deg C
SUBSTAGE(2) 36 hours, 90 deg C

PRO N 79902-59-3

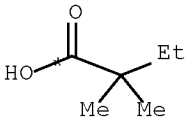
RX(12) OF 15 COMPOSED OF RX(1), RX(2), RX(3), RX(4)
RX(12) A + I + M ===> N



A

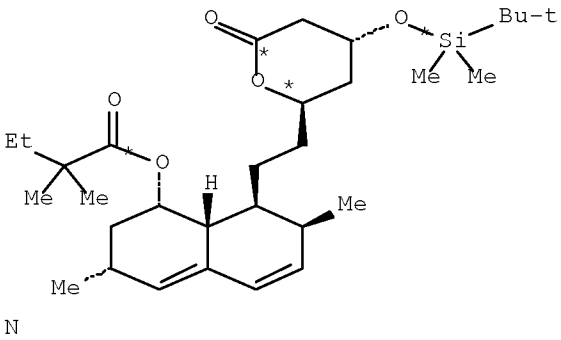


I



M

4
STEPS

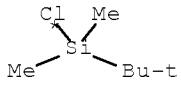


N

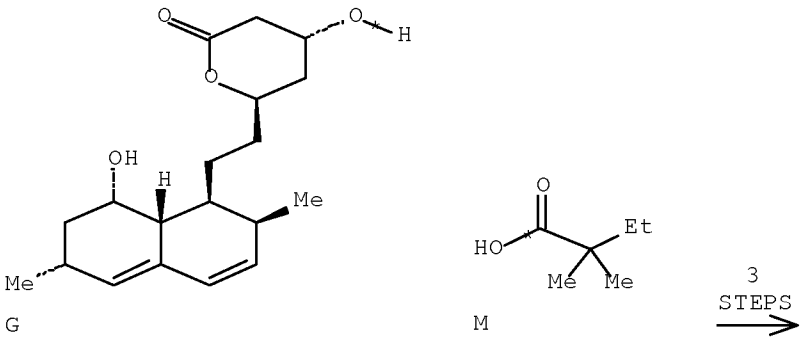
RX(1) RCT A 75330-75-5

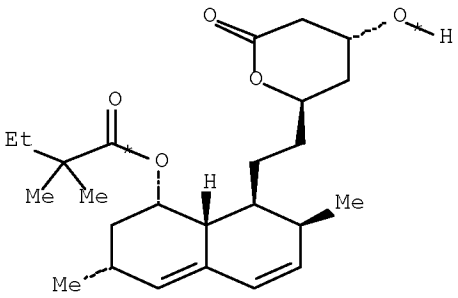
STAGE(1)
RGT C 1310-73-2 NaOH
SOL 67-56-1 MeOH
CON SUBSTAGE(1) 40 deg C
SUBSTAGE(2) 15 hours, 65 - 75 deg C

```
                    SUBSTAGE(3) 75 deg C -> 35 deg C

              STAGE(2)
                 RGT  D 7647-01-0 HCl
                 SOL  7732-18-5 Water
                 CON  SUBSTAGE(1) pH 7.5 - 8
                      SUBSTAGE(2) cooled, pH 1.5 - 2

           PRO  B 132748-10-8

RX(2)      RCT  B 132748-10-8
           PRO  G 79952-42-4
           SOL  7732-18-5 Water, 108-88-3 PhMe
           CON  SUBSTAGE(1) room temperature -> 110 deg C
                SUBSTAGE(2) 2 hours, reflux

RX(3)

              STAGE(1)
                 RGT  K 288-32-4 1H-Imidazole
                 SOL  68-12-2 DMF
                 CON  30 deg C -> 20 deg C

              STAGE(2)
                 RCT  I 18162-48-6
                 CON  15 - 20 deg C

              STAGE(3)
                 RCT  G 79952-42-4
                 SOL  68-12-2 DMF
                 CON  3 hours, 15 - 20 deg C

           PRO  J 79902-31-1

RX(4)      RCT  J 79902-31-1

              STAGE(1)
                 RGT  O 110-86-1 Pyridine
                 CAT  1122-58-3 4-DMAP
                 SOL  110-82-7 Cyclohexane
                 CON  15 minutes, 20 - 25 deg C

              STAGE(2)
                 RCT  M 595-37-9
                 SOL  110-82-7 Cyclohexane
                 CON  SUBSTAGE(1) 25 deg C -> 90 deg C
                      SUBSTAGE(2) 36 hours, 90 deg C

           PRO  N 79902-59-3


RX(13) OF 15 COMPOSED OF RX(3), RX(4), RX(5)
RX(13)     I  +  G  +  M  ===>  R
```



I





R
YIELD 95%

RX(3)

STAGE(1)
RGT K 288-32-4 1H-Imidazole
SOL 68-12-2 DMF
CON 30 deg C -> 20 deg C

STAGE(2)
RCT I 18162-48-6
CON 15 - 20 deg C

STAGE(3)
RCT G 79952-42-4
SOL 68-12-2 DMF
CON 3 hours, 15 - 20 deg C

PRO J 79902-31-1

RX(4) RCT J 79902-31-1

STAGE(1)

RGT O 110-86-1 Pyridine
CAT 1122-58-3 4-DMAP
SOL 110-82-7 Cyclohexane
CON 15 minutes, 20 - 25 deg C

STAGE(2)
RCT M 595-37-9
SOL 110-82-7 Cyclohexane
CON SUBSTAGE(1) 25 deg C -> 90 deg C
SUBSTAGE(2) 36 hours, 90 deg C

PRO N 79902-59-3

RX(5) RCT N 79902-59-3

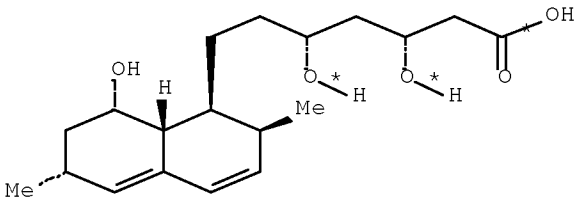
STAGE(1)
SOL 109-99-9 THF
CON 15 minutes, 25 - 35 deg C

STAGE(2)
RGT S 64-19-7 AcOH
SOL 7732-18-5 Water
CON 35 deg C -> 20 deg C

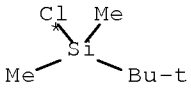
STAGE(3)
RGT T 429-41-4 Bu4N.F
SOL 109-99-9 THF
CON 30 - 35 hours, 18 - 22 deg C

PRO R 79902-63-9

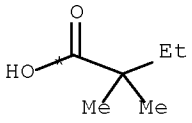
RX(14) OF 15 COMPOSED OF RX(2), RX(3), RX(4), RX(5)
RX(14) B + I + M ===> R



B

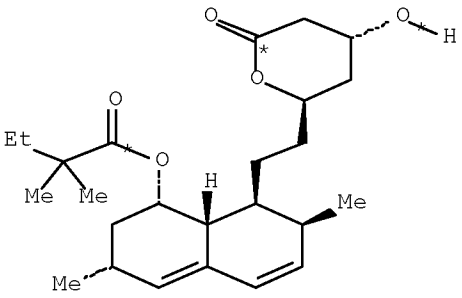


I



M

4
STEPS



R
YIELD 95%

RX(2) RCT B 132748-10-8
PRO G 79952-42-4
SOL 7732-18-5 Water, 108-88-3 PhMe
CON SUBSTAGE(1) room temperature -> 110 deg C
SUBSTAGE(2) 2 hours, reflux

RX(3)

STAGE(1)
RGT K 288-32-4 1H-Imidazole
SOL 68-12-2 DMF
CON 30 deg C -> 20 deg C

STAGE(2)
RCT I 18162-48-6
CON 15 - 20 deg C

STAGE(3)
RCT G 79952-42-4
SOL 68-12-2 DMF
CON 3 hours, 15 - 20 deg C

PRO J 79902-31-1

RX(4) RCT J 79902-31-1

STAGE(1)
RGT O 110-86-1 Pyridine
CAT 1122-58-3 4-DMAP
SOL 110-82-7 Cyclohexane
CON 15 minutes, 20 - 25 deg C

STAGE(2)
RCT M 595-37-9
SOL 110-82-7 Cyclohexane
CON SUBSTAGE(1) 25 deg C -> 90 deg C
SUBSTAGE(2) 36 hours, 90 deg C

PRO N 79902-59-3

RX(5) RCT N 79902-59-3

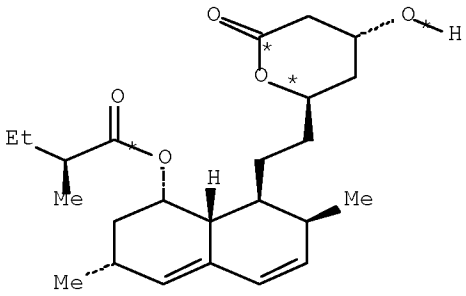
STAGE(1)
SOL 109-99-9 THF
CON 15 minutes, 25 - 35 deg C

STAGE(2)
RGT S 64-19-7 AcOH
SOL 7732-18-5 Water
CON 35 deg C -> 20 deg C

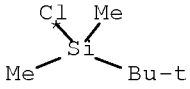
STAGE(3)
RGT T 429-41-4 Bu4N.F
SOL 109-99-9 THF
CON 30 - 35 hours, 18 - 22 deg C

PRO R 79902-63-9

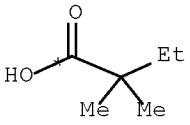
RX(15) OF 15 COMPOSED OF RX(1), RX(2), RX(3), RX(4), RX(5)
RX(15) A + I + M ===> R



A

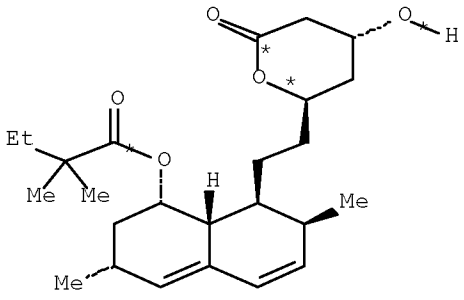


I



M

5
STEPS



R
YIELD 95%

RX(1) RCT A 75330-75-5

STAGE(1)

```
                RGT  C 1310-73-2 NaOH
                SOL  67-56-1 MeOH
                CON  SUBSTAGE(1) 40 deg C
                     SUBSTAGE(2) 15 hours, 65 - 75 deg C
                     SUBSTAGE(3) 75 deg C -> 35 deg C

             STAGE(2)
                RGT  D 7647-01-0 HCl
                SOL  7732-18-5 Water
                CON  SUBSTAGE(1) pH 7.5 - 8
                     SUBSTAGE(2) cooled, pH 1.5 - 2

          PRO  B 132748-10-8

RX(2)     RCT  B 132748-10-8
          PRO  G 79952-42-4
          SOL  7732-18-5 Water, 108-88-3 PhMe
          CON  SUBSTAGE(1) room temperature -> 110 deg C
               SUBSTAGE(2) 2 hours, reflux

RX(3)

             STAGE(1)
                RGT  K 288-32-4 1H-Imidazole
                SOL  68-12-2 DMF
                CON  30 deg C -> 20 deg C

             STAGE(2)
                RCT  I 18162-48-6
                CON  15 - 20 deg C

             STAGE(3)
                RCT  G 79952-42-4
                SOL  68-12-2 DMF
                CON  3 hours, 15 - 20 deg C

          PRO  J 79902-31-1

RX(4)     RCT  J 79902-31-1

             STAGE(1)
                RGT  O 110-86-1 Pyridine
                CAT  1122-58-3 4-DMAP
                SOL  110-82-7 Cyclohexane
                CON  15 minutes, 20 - 25 deg C

             STAGE(2)
                RCT  M 595-37-9
                SOL  110-82-7 Cyclohexane
                CON  SUBSTAGE(1) 25 deg C -> 90 deg C
                     SUBSTAGE(2) 36 hours, 90 deg C

          PRO  N 79902-59-3

RX(5)     RCT  N 79902-59-3

             STAGE(1)
                SOL  109-99-9 THF
                CON  15 minutes, 25 - 35 deg C
```

STAGE(2)
RGT S 64-19-7 AcOH
SOL 7732-18-5 Water
CON 35 deg C -> 20 deg C

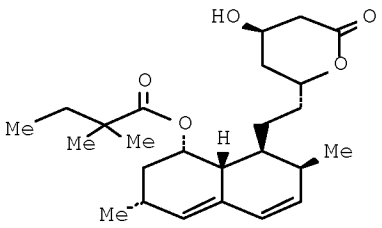
STAGE(3)
RGT T 429-41-4 Bu4N.F
SOL 109-99-9 THF
CON 30 - 35 hours, 18 - 22 deg C

PRO R 79902-63-9

L150 ANSWER 3 OF 29 CASREACT COPYRIGHT 2009 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 147:522019 CASREACT Full-text
TITLE: Procedure for the obtention of simvastatin
INVENTOR(S): Coca Benito, Raquel; Requena Perez, Felipe; Diaz Tejo, Luis; Asensio Dominguez, Ramon; Faja Genoves, Montserrat; Vilarrasa Llorens, Jaume; Cruzado Rodriguez, M. Carmen; Puerta Gochi, M. Carmen
PATENT ASSIGNEE(S): Ercros Industrial S A, Spain
SOURCE: Span., 18pp.
CODEN: SPXXAD
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
ES 2239543	A1	20050916	ES 2004-633	20040315
ES 2239543	B1	20060801		

PRIORITY APPLN. INFO.: ES 2004-633 20040315
GI

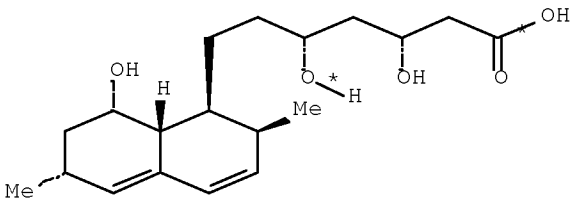


I

AB The production of an HMG-CoA reductase inhibitor has the product, simvastatin (I), obtained by lactonizing under mild acid conditions. Protection by triethylsilyl chloride, acylation in the presence of 4-dimethylaminopyridine, and release from protection by e.g. diisopropylethylamine trihydrofluoride yields high-purity product of low secondary products content. Thus, I was prepared from lovastatin via saponification with aqueous KOH to give the deacyl acid, lactonization with aqueous HCl in CH2Cl2, silylation with Et3SiCl in CH2Cl2 containing 4-DMAP, acylation with dimethylbutyryl chloride in CH2Cl2

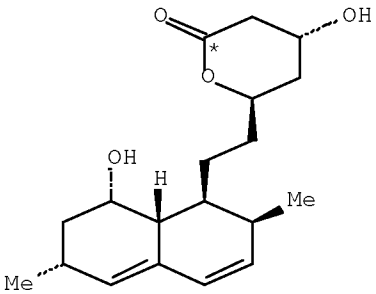
containing 4-DMAP, desilylation with HF in EtOAc, and recrystn. from MeOH. Alternatively, the deacyl acid can be obtained from an Aspergillus terreus fermentation broth for the production of lovastatin and can be converted to I following the procedure above.

RX(1) OF 15 A ===> B...



A

(1)



B

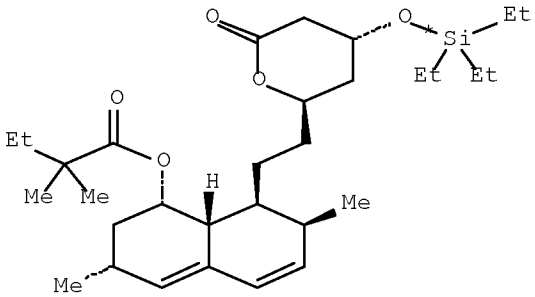
RX(1) RCT A 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON 25 deg C

STAGE(2)
RGT C 7647-01-0 HCl
SOL 7732-18-5 Water
CON 25 deg C, pH 2.5

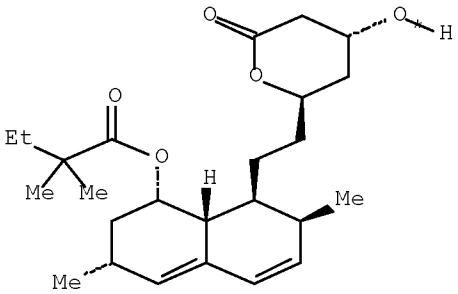
PRO B 79952-42-4

RX(4) OF 15 ...J ===> K



J

(4) →



K

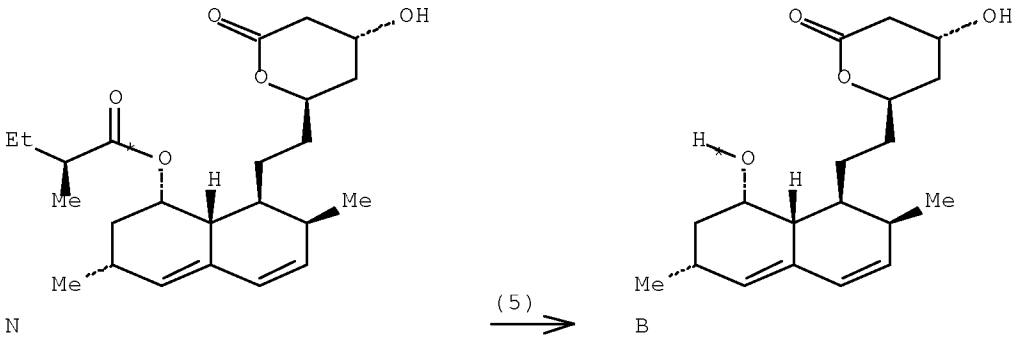
RX(4) RCT J 956218-19-2

STAGE(1)
SOL 141-78-6 AcOEt
CON 20 - 25 deg C

STAGE(2)
RGT L 131600-43-6 2-Propanamine, N-ethyl-N-(1-methylethyl)-, hydrofluoride (1:3)
CON 2 - 3 hours, 20 - 25 deg C

PRO K 79902-63-9

RX(5) OF 15 N ===> B...



N B

RX(5) RCT N 75330-75-5

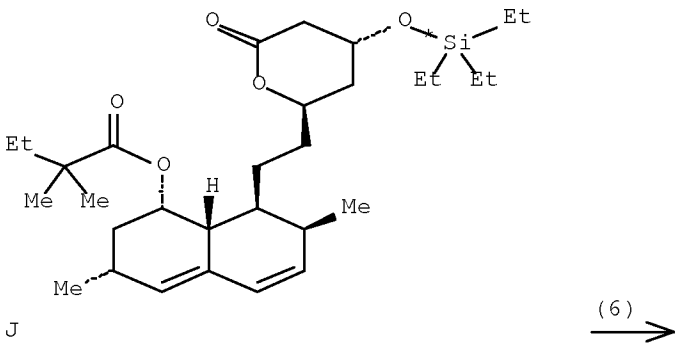
STAGE(1)
RGT O 1310-58-3 KOH
SOL 7732-18-5 Water
CON 72 hours, reflux

STAGE(2)
SOL 75-09-2 CH2Cl2
CON 25 deg C

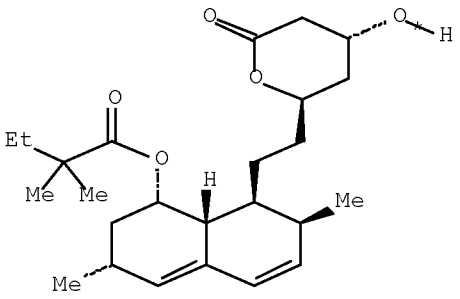
STAGE(3)
RGT C 7647-01-0 HCl
SOL 7732-18-5 Water
CON 25 deg C, pH 2.5

PRO B 79952-42-4

RX(6) OF 15 J ===> K



J



K

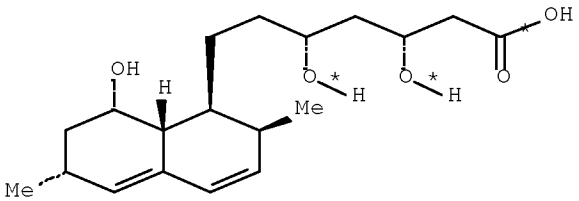
RX(6) RCT J 956218-19-2

STAGE(1)
SOL 141-78-6 AcOEt
CON 20 - 25 deg C

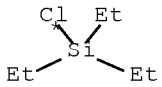
STAGE(2)
RGT P 7664-39-3 HF
CON - 2 hour, 20 - 25 deg C

PRO K 79902-63-9

RX(7) OF 15 COMPOSED OF RX(1), RX(2)
RX(7) A + F ===> G

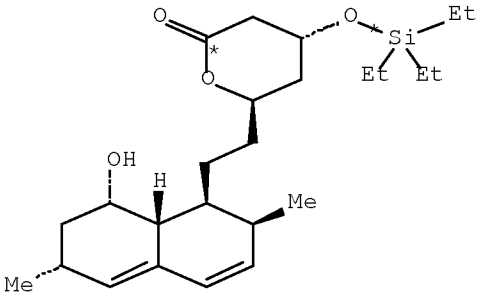


A



F

2 STEPS



G

RX(1) RCT A 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON 25 deg C

STAGE(2)
RGT C 7647-01-0 HCl
SOL 7732-18-5 Water
CON 25 deg C, pH 2.5

PRO B 79952-42-4

RX(2) RCT B 79952-42-4

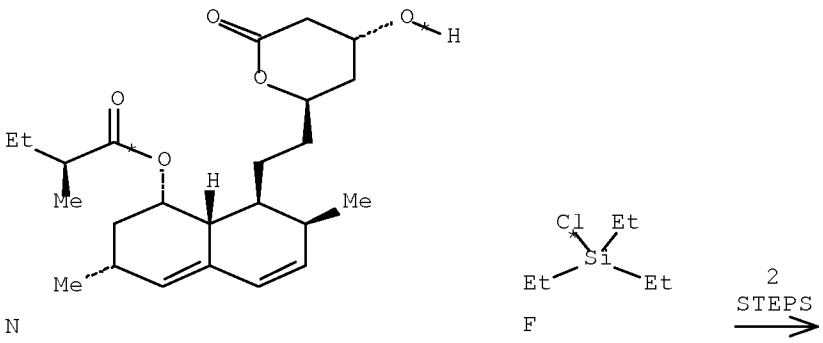
STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature -> -10 deg C

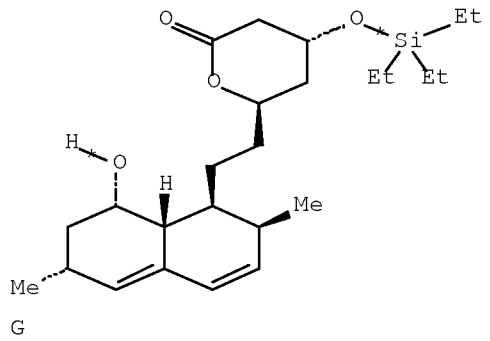
STAGE(2)
RGT H 1122-58-3 4-DMAP
CON -10 - -5 deg C

STAGE(3)
RCT F 994-30-9
CON 6 hours, -10 - -5 deg C

PRO G 863108-10-5

RX(8) OF 15 COMPOSED OF RX(5), RX(2)
RX(8) N + F ===> G





G

RX(5) RCT N 75330-75-5

STAGE(1)
RGT O 1310-58-3 KOH
SOL 7732-18-5 Water
CON 72 hours, reflux

STAGE(2)
SOL 75-09-2 CH2Cl2
CON 25 deg C

STAGE(3)
RGT C 7647-01-0 HCl
SOL 7732-18-5 Water
CON 25 deg C, pH 2.5

PRO B 79952-42-4

RX(2) RCT B 79952-42-4

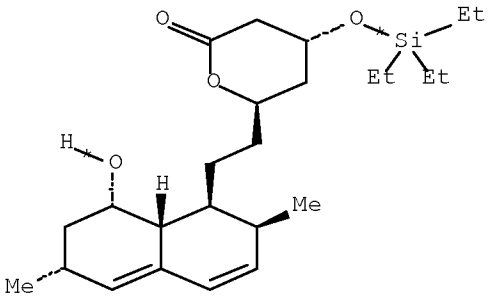
STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature -> -10 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON -10 - -5 deg C

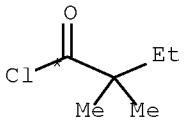
STAGE(3)
RCT F 994-30-9
CON 6 hours, -10 - -5 deg C

PRO G 863108-10-5

RX(10) OF 15 COMPOSED OF RX(3), RX(4)
RX(10) G + I ===> K

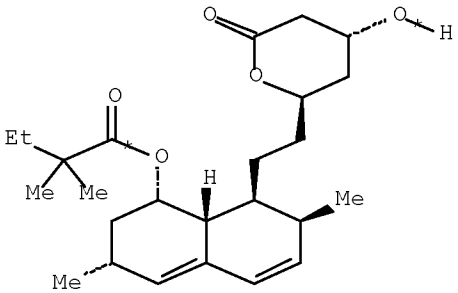


G



I

2
STEPS



K

RX(3) RCT G 863108-10-5

STAGE(1)
SOL 75-09-2 CH2Cl2
CON 20 - 25 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON 20 - 25 deg C

STAGE(3)
RCT I 5856-77-9
CON SUBSTAGE(1) 20 - 25 deg C -> reflux
SUBSTAGE(2) 3 hours, reflux

PRO J 956218-19-2

RX(4) RCT J 956218-19-2

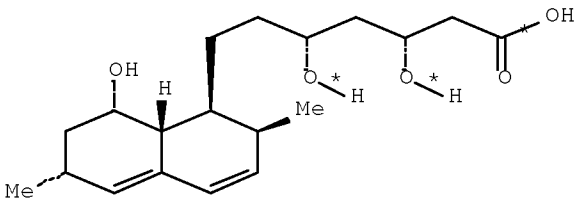
STAGE(1)
SOL 141-78-6 AcOEt
CON 20 - 25 deg C

STAGE(2)
RGT L 131600-43-6 2-Propanamine, N-ethyl-N-(1-methylethyl)-,

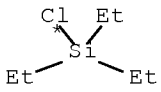
hydrofluoride (1:3)
CON 2 - 3 hours, 20 - 25 deg C

PRO K 79902-63-9

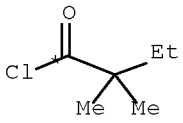
RX(11) OF 15 COMPOSED OF RX(1), RX(2), RX(3)
RX(11) A + F + I ===> J



A

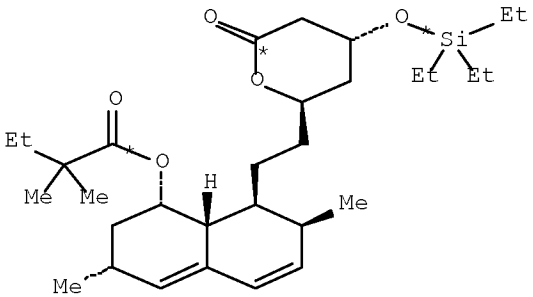


F



I

3
STEPS



J

RX(1) RCT A 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON 25 deg C

STAGE(2)
RGT C 7647-01-0 HCl
SOL 7732-18-5 Water
CON 25 deg C, pH 2.5

PRO B 79952-42-4

RX(2) RCT B 79952-42-4

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature -> -10 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON -10 - -5 deg C

STAGE(3)
RCT F 994-30-9
CON 6 hours, -10 - -5 deg C

PRO G 863108-10-5

RX(3) RCT G 863108-10-5

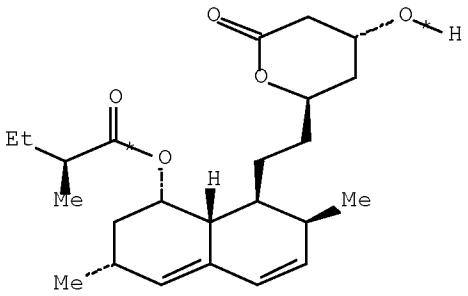
STAGE(1)
SOL 75-09-2 CH2Cl2
CON 20 - 25 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON 20 - 25 deg C

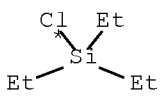
STAGE(3)
RCT I 5856-77-9
CON SUBSTAGE(1) 20 - 25 deg C -> reflux
SUBSTAGE(2) 3 hours, reflux

PRO J 956218-19-2

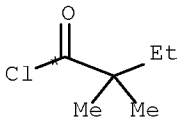
RX(12) OF 15 COMPOSED OF RX(5), RX(2), RX(3)
RX(12) N + F + I ===> J



N

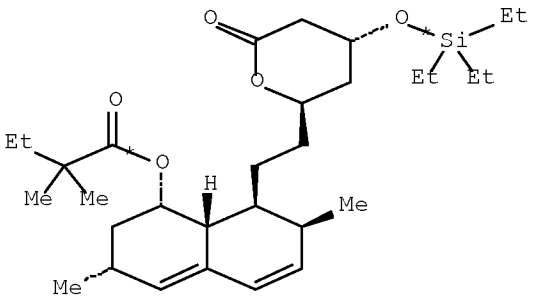


F



I

3
STEPS
→



J

RX(5) RCT N 75330-75-5

STAGE(1)
RGT O 1310-58-3 KOH
SOL 7732-18-5 Water
CON 72 hours, reflux

STAGE(2)
SOL 75-09-2 CH2Cl2
CON 25 deg C

STAGE(3)
RGT C 7647-01-0 HCl
SOL 7732-18-5 Water
CON 25 deg C, pH 2.5

PRO B 79952-42-4

RX(2) RCT B 79952-42-4

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature -> -10 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON -10 - -5 deg C

STAGE(3)
RCT F 994-30-9
CON 6 hours, -10 - -5 deg C

PRO G 863108-10-5

RX(3) RCT G 863108-10-5

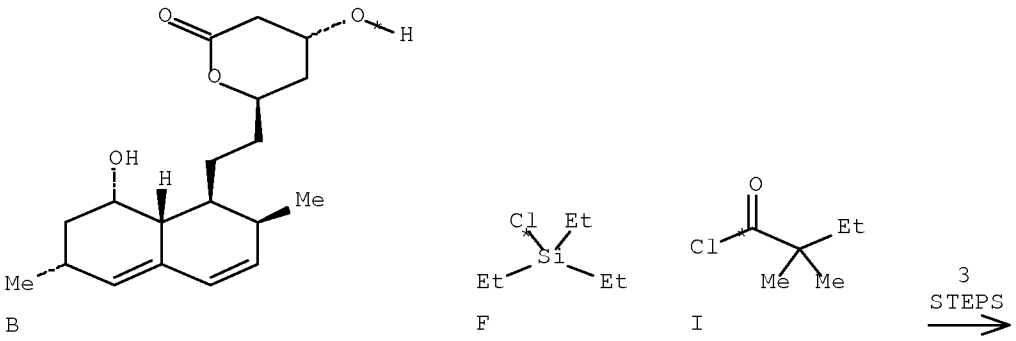
STAGE(1)
SOL 75-09-2 CH2Cl2
CON 20 - 25 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON 20 - 25 deg C

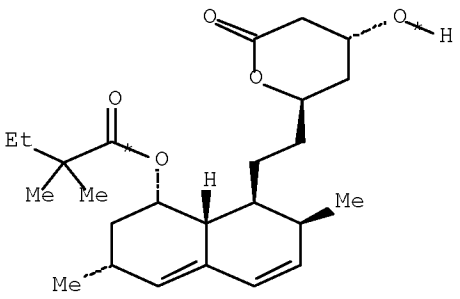
STAGE(3)
RCT I 5856-77-9
CON SUBSTAGE(1) 20 - 25 deg C -> reflux
SUBSTAGE(2) 3 hours, reflux

PRO J 956218-19-2

RX(13) OF 15 COMPOSED OF RX(2), RX(3), RX(4)
RX(13) B + F + I ===> K



B F I



K

RX(2) RCT B 79952-42-4

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature -> -10 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON -10 - -5 deg C

STAGE(3)
RCT F 994-30-9
CON 6 hours, -10 - -5 deg C

PRO G 863108-10-5

RX(3) RCT G 863108-10-5

STAGE(1)
SOL 75-09-2 CH2Cl2
CON 20 - 25 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON 20 - 25 deg C

STAGE(3)
RCT I 5856-77-9
CON SUBSTAGE(1) 20 - 25 deg C -> reflux
SUBSTAGE(2) 3 hours, reflux

PRO J 956218-19-2

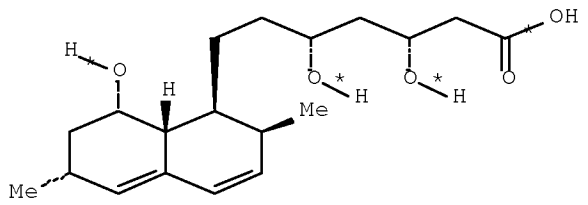
RX(4) RCT J 956218-19-2

STAGE(1)
SOL 141-78-6 AcOEt
CON 20 - 25 deg C

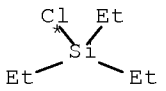
STAGE(2)
RGT L 131600-43-6 2-Propanamine, N-ethyl-N-(1-methylethyl)-, hydrofluoride (1:3)
CON 2 - 3 hours, 20 - 25 deg C

PRO K 79902-63-9

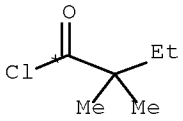
RX(14) OF 15 COMPOSED OF RX(1), RX(2), RX(3), RX(4)
RX(14) A + F + I ===> K



A

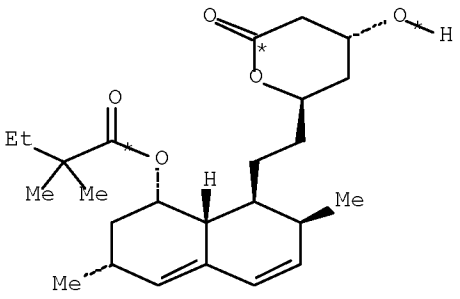


F



I

4
STEPS
→



K

RX(1) RCT A 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON 25 deg C

STAGE(2)
RGT C 7647-01-0 HCl
SOL 7732-18-5 Water
CON 25 deg C, pH 2.5

PRO B 79952-42-4

RX(2) RCT B 79952-42-4

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature -> -10 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON -10 - -5 deg C

STAGE(3)
RCT F 994-30-9
CON 6 hours, -10 - -5 deg C

PRO G 863108-10-5

RX(3) RCT G 863108-10-5

STAGE(1)
SOL 75-09-2 CH2Cl2
CON 20 - 25 deg C

STAGE(2)
RGT H 1122-58-3 4-DMAP
CON 20 - 25 deg C

STAGE(3)

RCT I 5856-77-9
CON SUBSTAGE(1) 20 - 25 deg C -> reflux
SUBSTAGE(2) 3 hours, reflux

PRO J 956218-19-2

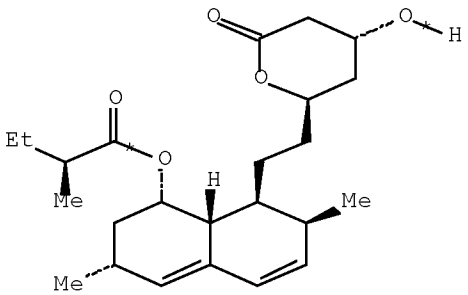
RX(4) RCT J 956218-19-2

STAGE(1)
SOL 141-78-6 AcOEt
CON 20 - 25 deg C

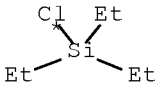
STAGE(2)
RGT L 131600-43-6 2-Propanamine, N-ethyl-N-(1-methylethyl)-, hydrofluoride (1:3)
CON 2 - 3 hours, 20 - 25 deg C

PRO K 79902-63-9

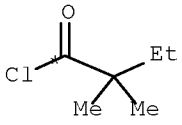
RX(15) OF 15 COMPOSED OF RX(5), RX(2), RX(3), RX(4)
RX(15) N + F + I ===> K



N

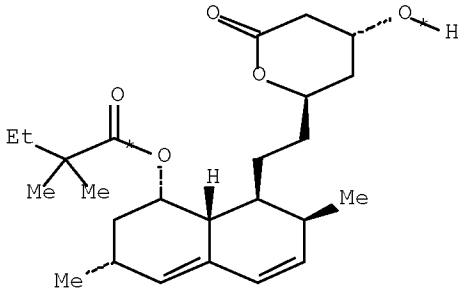


F



I

4
STEPS



K

RX(5) RCT N 75330-75-5

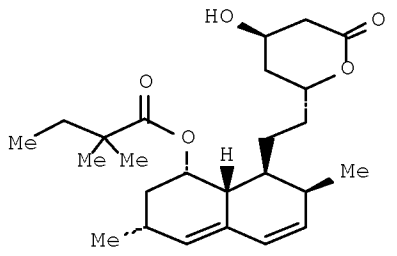
```
            STAGE(1)
               RGT  O 1310-58-3 KOH
               SOL  7732-18-5 Water
               CON  72 hours, reflux

            STAGE(2)
               SOL  75-09-2 CH2Cl2
               CON  25 deg C

            STAGE(3)
               RGT  C 7647-01-0 HCl
               SOL  7732-18-5 Water
               CON  25 deg C, pH 2.5

         PRO  B 79952-42-4

RX(2)    RCT  B 79952-42-4

            STAGE(1)
               SOL  75-09-2 CH2Cl2
               CON  room temperature -> -10 deg C

            STAGE(2)
               RGT  H 1122-58-3 4-DMAP
               CON  -10 - -5 deg C

            STAGE(3)
               RCT  F 994-30-9
               CON  6 hours, -10 - -5 deg C

         PRO  G 863108-10-5

RX(3)    RCT  G 863108-10-5

            STAGE(1)
               SOL  75-09-2 CH2Cl2
               CON  20 - 25 deg C

            STAGE(2)
               RGT  H 1122-58-3 4-DMAP
               CON  20 - 25 deg C

            STAGE(3)
               RCT  I 5856-77-9
               CON  SUBSTAGE(1) 20 - 25 deg C -> reflux
                    SUBSTAGE(2) 3 hours, reflux

         PRO  J 956218-19-2

RX(4)    RCT  J 956218-19-2

            STAGE(1)
               SOL  141-78-6 AcOEt
               CON  20 - 25 deg C

            STAGE(2)
               RGT  L 131600-43-6 2-Propanamine, N-ethyl-N-(1-methylethyl)-,
                    hydrofluoride (1:3)
               CON  2 - 3 hours, 20 - 25 deg C
```

PRO K 79902-63-9

L150 ANSWER 4 OF 29 CASREACT COPYRIGHT 2009 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 139:100975 CASREACT Full-text
TITLE: Process for the preparation of simvastatin
INVENTOR(S): Lee, Jaeheon; Ha, Taehee; Park, Chulhyun; Lee, Hoechul; Lee, Gwansun; Chang, Youngkil
PATENT ASSIGNEE(S): Hanmi Pharm. Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057684	A1	20030717	WO 2002-KR2434	20021226
W: AU, CA, CN, HU, IN, JP, US				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR				
KR 2003060425	A	20030716	KR 2002-1118	20020109
AU 2002359034	A1	20030724	AU 2002-359034	20021226
EP 1463723	A1	20041006	EP 2002-793514	20021226
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, CY, TR, BG, CZ, EE, SK				
CN 1612872	A	20050504	CN 2002-826896	20021226
CN 1283633	C	20061108		
JP 2005514419	T	20050519	JP 2003-557999	20021226
JP 4216727	B2	20090128		
US 20050080275	A1	20050414	US 2004-501007	20040708
US 7528265	B2	20090505		
PRIORITY APPLN. INFO.:			KR 2002-1118	20020109
			WO 2002-KR2434	20021226

OTHER SOURCE(S): MARPAT 139:100975
GI



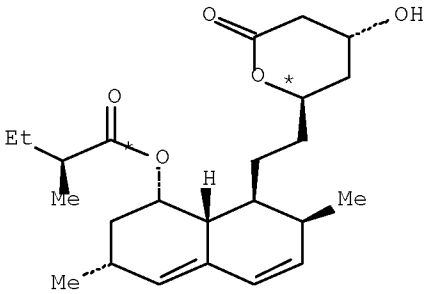
I

AB Highly pure simvastatin (I) can be prepared economically in a high yield using the method comprising the steps of treating lovastatin with potassium hydroxide dissolved in a mixture of water and methanol to obtain a triol acid; relactonizing the triol acid, and protecting the hydroxy group on the lactone ring; and acylating the resulting compound with 2,2-dimethylbutyryl chloride or 2,2-dimethylbutyryl bromide in the presence of an acylation catalyst in an

organic solvent, followed by removing the silyl protecting group on the lactone ring to obtain simvastatin.

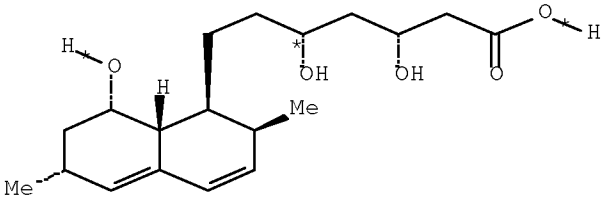
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RX(1) OF 15 A ===> B...



A

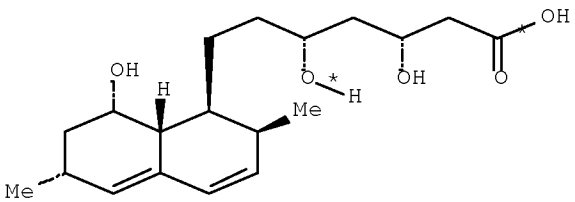
(1)



B
YIELD 98%

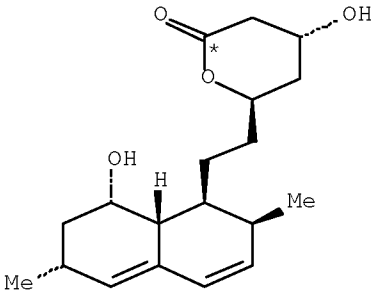
RX(1) RCT A 75330-75-5
RGT C 1310-58-3 KOH
PRO B 132748-10-8
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 8 hours, reflux

RX(2) OF 15 ...B ===> F...



B

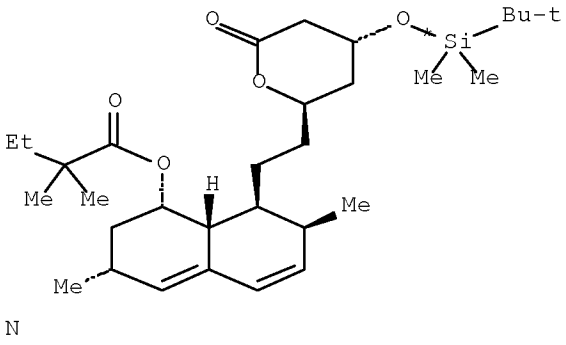
(2)



F
YIELD 98%

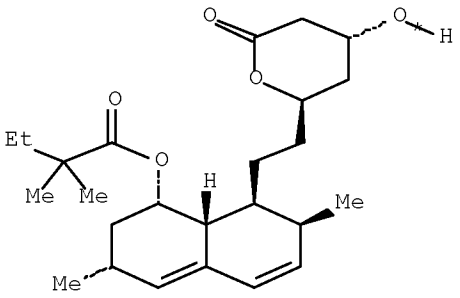
RX(2) RCT B 132748-10-8
RGT G 104-15-4 TsOH
PRO F 79952-42-4
SOL 141-78-6 AcOEt
CON 3 hours, room temperature

RX(5) OF 15 ...N ===> R



N

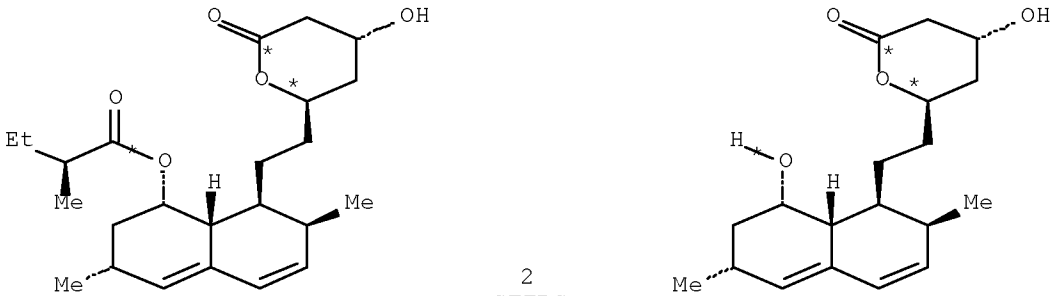
(5)



R
YIELD 91%

RX(5) RCT N 79902-59-3
RGT S 429-41-4 Bu4N.F
PRO R 79902-63-9
SOL 109-99-9 THF, 64-19-7 AcOH
CON 48 hours, room temperature

RX(6) OF 15 COMPOSED OF RX(1), RX(2)
RX(6) A ===> F



A

2 STEPS

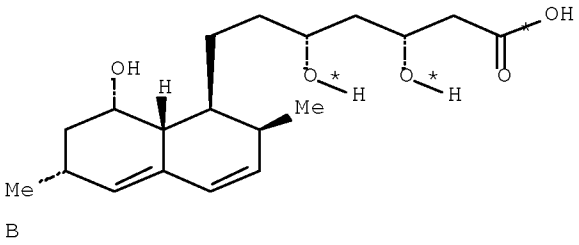
F
YIELD 98%

RX(1) RCT A 75330-75-5
RGT C 1310-58-3 KOH
PRO B 132748-10-8
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 8 hours, reflux

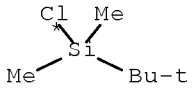
RX(2) RCT B 132748-10-8
RGT G 104-15-4 TsOH
PRO F 79952-42-4
SOL 141-78-6 AcOEt
CON 3 hours, room temperature

RX(7) OF 15 COMPOSED OF RX(2), RX(3)

RX(7) B + I ===> J

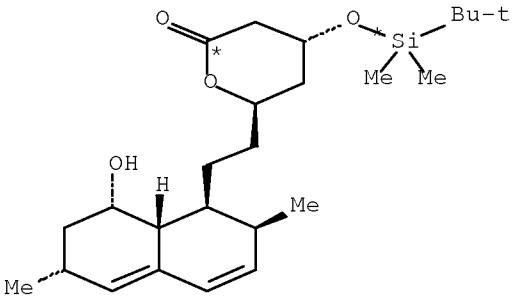


B



I

2 STEPS

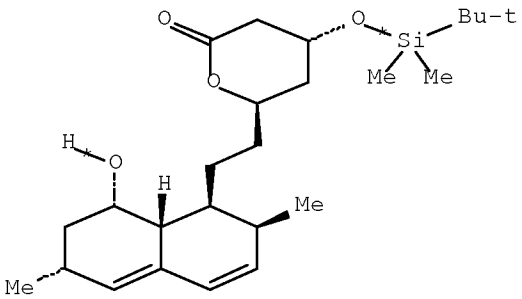


J
YIELD 96%

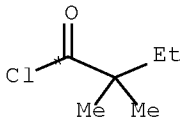
RX(2) RCT B 132748-10-8
RGT G 104-15-4 TsOH
PRO F 79952-42-4
SOL 141-78-6 AcOEt
CON 3 hours, room temperature

RX(3) RCT F 79952-42-4, I 18162-48-6
RGT K 288-32-4 1H-Imidazole
PRO J 79902-31-1
SOL 75-09-2 CH2Cl2
CON 6 hours, 30 deg C

RX(9) OF 15 COMPOSED OF RX(4), RX(5)
RX(9) J + M ===> R

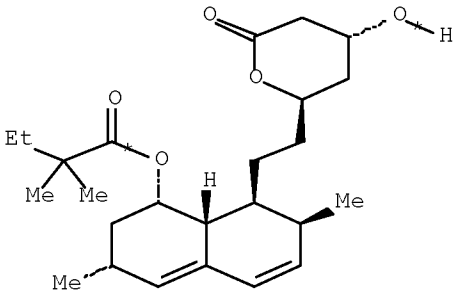


J



M

2 STEPS

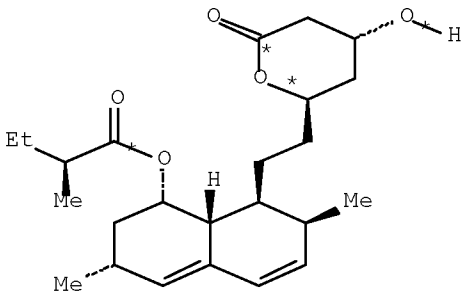


R
YIELD 91%

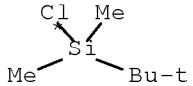
RX(4) RCT J 79902-31-1, M 5856-77-9
RGT O 25316-59-0 Bu3NCH2Ph.Br, P 110-86-1 Pyridine
PRO N 79902-59-3
SOL 71-43-2 Benzene
CON 30 minutes, reflux

RX(5) RCT N 79902-59-3
RGT S 429-41-4 Bu4N.F
PRO R 79902-63-9
SOL 109-99-9 THF, 64-19-7 AcOH
CON 48 hours, room temperature

RX(10) OF 15 COMPOSED OF RX(1), RX(2), RX(3)
RX(10) A + I ===> J

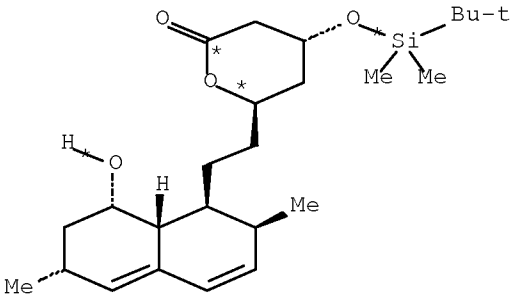


A



I

3
STEPS



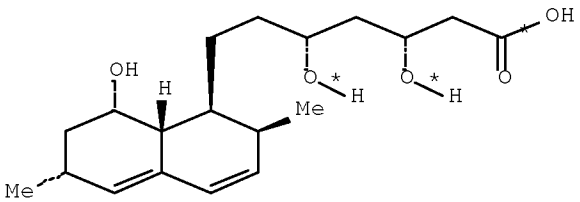
J
YIELD 96%

RX(1) RCT A 75330-75-5
RGT C 1310-58-3 KOH
PRO B 132748-10-8
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 8 hours, reflux

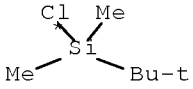
RX(2) RCT B 132748-10-8
RGT G 104-15-4 TsOH
PRO F 79952-42-4
SOL 141-78-6 AcOEt
CON 3 hours, room temperature

RX(3) RCT F 79952-42-4, I 18162-48-6
RGT K 288-32-4 1H-Imidazole
PRO J 79902-31-1
SOL 75-09-2 CH2Cl2
CON 6 hours, 30 deg C

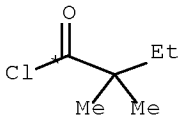
RX(11) OF 15 COMPOSED OF RX(2), RX(3), RX(4)
RX(11) B + I + M ===> N



B

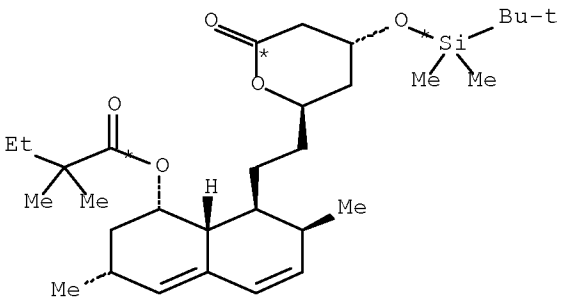


I



M

3
STEPS



N
YIELD 98%

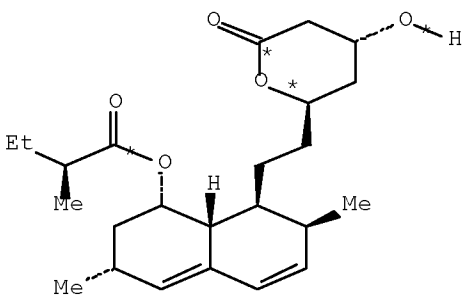
RX(2) RCT B 132748-10-8
RGT G 104-15-4 TsOH
PRO F 79952-42-4
SOL 141-78-6 AcOEt
CON 3 hours, room temperature

RX(3) RCT F 79952-42-4, I 18162-48-6
RGT K 288-32-4 1H-Imidazole
PRO J 79902-31-1
SOL 75-09-2 CH2Cl2
CON 6 hours, 30 deg C

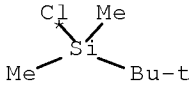
RX(4) RCT J 79902-31-1, M 5856-77-9
RGT O 25316-59-0 Bu3NCH2Ph.Br, P 110-86-1 Pyridine
PRO N 79902-59-3
SOL 71-43-2 Benzene
CON 30 minutes, reflux

RX(12) OF 15 COMPOSED OF RX(1), RX(2), RX(3), RX(4)

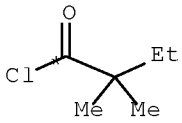
RX(12) A + I + M ===> N



A

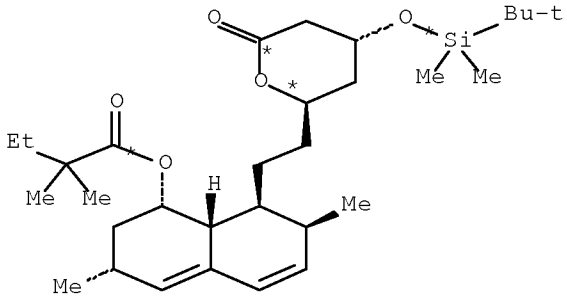


I



M

4 STEPS



N
YIELD 98%

RX(1) RCT A 75330-75-5
RGT C 1310-58-3 KOH
PRO B 132748-10-8
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 8 hours, reflux

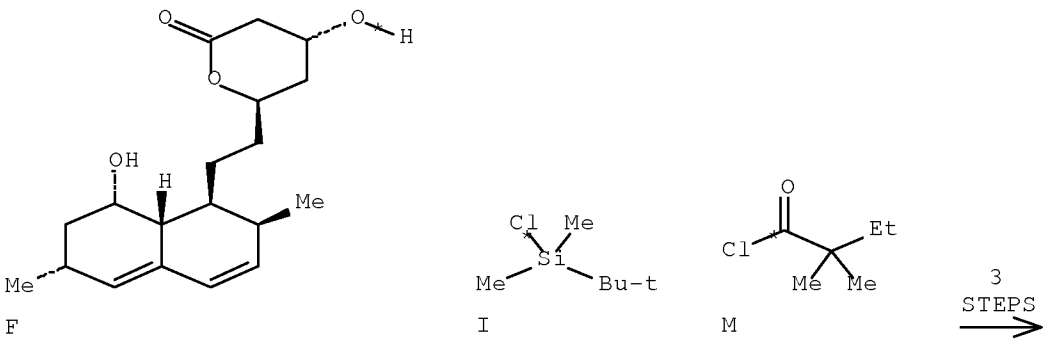
RX(2) RCT B 132748-10-8
RGT G 104-15-4 TsOH
PRO F 79952-42-4
SOL 141-78-6 AcOEt
CON 3 hours, room temperature

RX(3) RCT F 79952-42-4, I 18162-48-6
RGT K 288-32-4 1H-Imidazole
PRO J 79902-31-1
SOL 75-09-2 CH2Cl2
CON 6 hours, 30 deg C

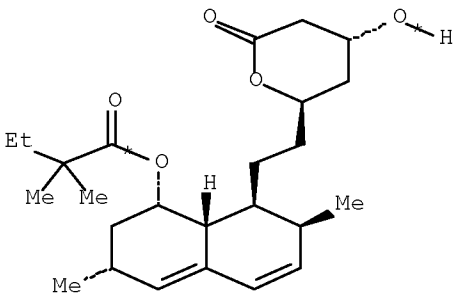
RX(4) RCT J 79902-31-1, M 5856-77-9
RGT O 25316-59-0 Bu3NCH2Ph.Br, P 110-86-1 Pyridine
PRO N 79902-59-3
SOL 71-43-2 Benzene

CON 30 minutes, reflux

RX(13) OF 15 COMPOSED OF RX(3), RX(4), RX(5)
RX(13) F + I + M ===> R



F I M



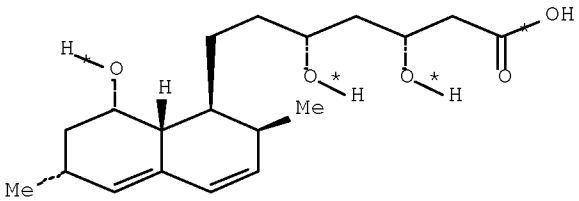
R
YIELD 91%

RX(3) RCT F 79952-42-4, I 18162-48-6
RGT K 288-32-4 1H-Imidazole
PRO J 79902-31-1
SOL 75-09-2 CH2Cl2
CON 6 hours, 30 deg C

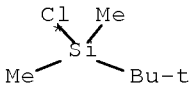
RX(4) RCT J 79902-31-1, M 5856-77-9
RGT O 25316-59-0 Bu3NCH2Ph.Br, P 110-86-1 Pyridine
PRO N 79902-59-3
SOL 71-43-2 Benzene
CON 30 minutes, reflux

RX(5) RCT N 79902-59-3
RGT S 429-41-4 Bu4N.F
PRO R 79902-63-9
SOL 109-99-9 THF, 64-19-7 AcOH
CON 48 hours, room temperature

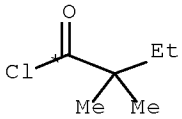
RX(14) OF 15 COMPOSED OF RX(2), RX(3), RX(4), RX(5)
RX(14) B + I + M ===> R



B

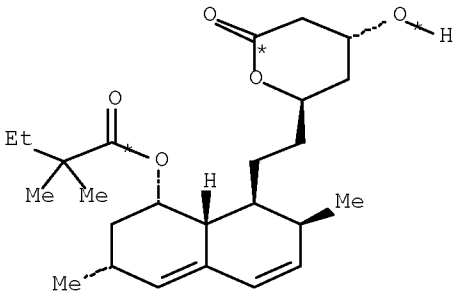


I



M

4
STEPS



R
YIELD 91%

RX(2) RCT B 132748-10-8
RGT G 104-15-4 TsOH
PRO F 79952-42-4
SOL 141-78-6 AcOEt
CON 3 hours, room temperature

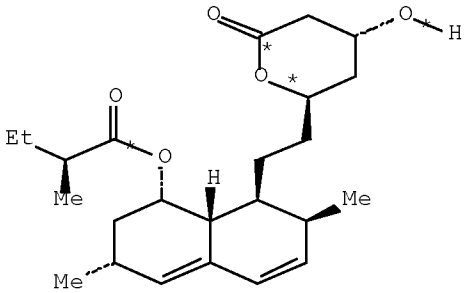
RX(3) RCT F 79952-42-4, I 18162-48-6
RGT K 288-32-4 1H-Imidazole
PRO J 79902-31-1
SOL 75-09-2 CH2Cl2
CON 6 hours, 30 deg C

RX(4) RCT J 79902-31-1, M 5856-77-9
RGT O 25316-59-0 Bu3NCH2Ph.Br, P 110-86-1 Pyridine
PRO N 79902-59-3

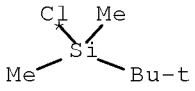
SOL 71-43-2 Benzene
CON 30 minutes, reflux

RX(5) RCT N 79902-59-3
RGT S 429-41-4 Bu4N.F
PRO R 79902-63-9
SOL 109-99-9 THF, 64-19-7 AcOH
CON 48 hours, room temperature

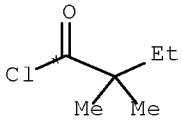
RX(15) OF 15 COMPOSED OF RX(1), RX(2), RX(3), RX(4), RX(5)
RX(15) A + I + M ===> R



A

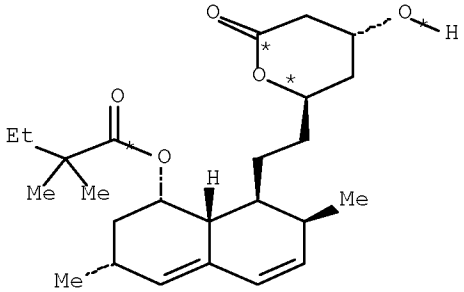


I



M

5
STEPS



R
YIELD 91%

RX(1) RCT A 75330-75-5
RGT C 1310-58-3 KOH
PRO B 132748-10-8
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 8 hours, reflux

RX(2) RCT B 132748-10-8
RGT G 104-15-4 TsOH
PRO F 79952-42-4
SOL 141-78-6 AcOEt

CON 3 hours, room temperature

RX(3) RCT F 79952-42-4, I 18162-48-6
RGT K 288-32-4 1H-Imidazole
PRO J 79902-31-1
SOL 75-09-2 CH2Cl2
CON 6 hours, 30 deg C

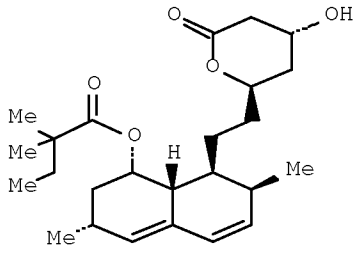
RX(4) RCT J 79902-31-1, M 5856-77-9
RGT O 25316-59-0 Bu3NCH2Ph.Br, P 110-86-1 Pyridine
PRO N 79902-59-3
SOL 71-43-2 Benzene
CON 30 minutes, reflux

RX(5) RCT N 79902-59-3
RGT S 429-41-4 Bu4N.F
PRO R 79902-63-9
SOL 109-99-9 THF, 64-19-7 AcOH
CON 48 hours, room temperature

L150 ANSWER 5 OF 29 CASREACT COPYRIGHT 2009 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 135:61179 CASREACT Full-text
TITLE: An improved process for preparing simvastatin
INVENTOR(S): Hong, Chung Il; Kim, Jung Woo; Shin, Hee Jong; Kang, Tae Won; Cho, Dong Ock
PATENT ASSIGNEE(S): Chong Kun Dang Pharmaceutical Corp., S. Korea
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045484	A2	20010628	WO 2001-KR301	20010227
WO 2001045484	A3	20020328		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2438477	A1	20010628	CA 2001-2438477	20010227
AU 2001037752	A	20010703	AU 2001-37752	20010227
JP 2004524260	T	20040812	JP 2001-546231	20010227
US 20040068123	A1	20040408	US 2003-468852	20030825
US 6833461	B2	20041221		
PRIORITY APPLN. INFO.:			WO 2001-KR301	20010227

GI

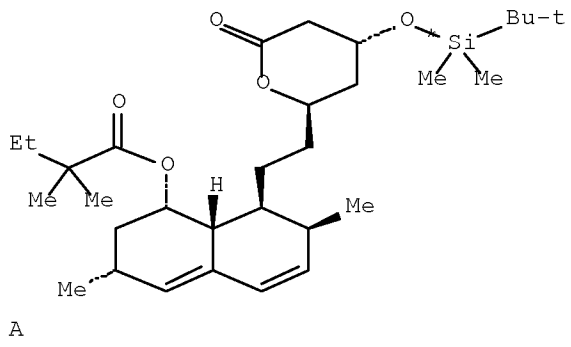


I

AB Simvastatin (I) was prepared with high yield and high purity by performing the following sequential processes comprising: (i) hydrolysis of lovastatin as starting material with potassium t-butoxide in an organic solvent and small amount of water under a mild reaction condition, followed by lactonization of the obtained solid intermediate with preventing from formation of byproducts; (ii) protection of an alc. group with t-butyldim ethylsilyl group which can be easily removed with concentrated hydrochloric acid without the formation of byproducts; (iii) acylation of the obtained protected intermediate with acyloxytriphenyl phosphonium salt as an acylating agent under a mild reaction condition; and (iv) removal of the silyl protective group with a concentrated hydrochloric acid. The improved process of preparing simvastatin is environmentally sound, economically efficient, and industrially useful.

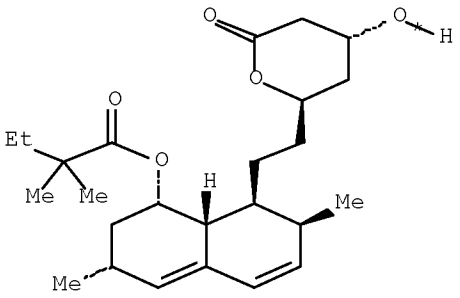
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RX(1) OF 15 ...A ===> R



A

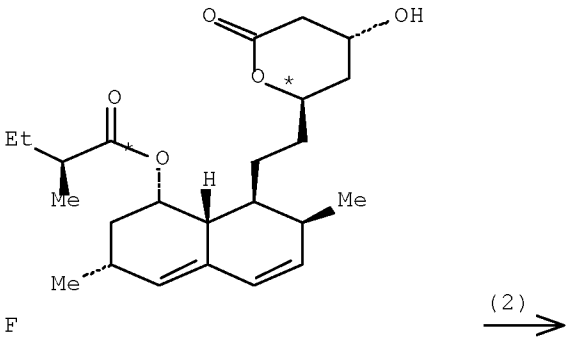
(1)



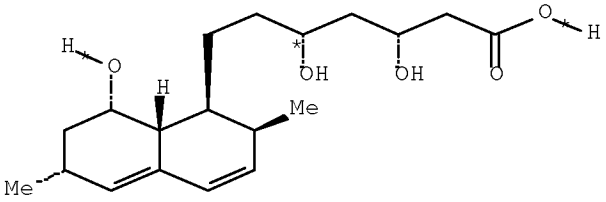
B
YIELD 92%

RX(1) RCT A 79902-59-3
RGT C 7647-01-0 HCl
PRO B 79902-63-9
SOL 109-99-9 THF, 123-91-1 Dioxane

RX(2) OF 15 E ===> G..



F

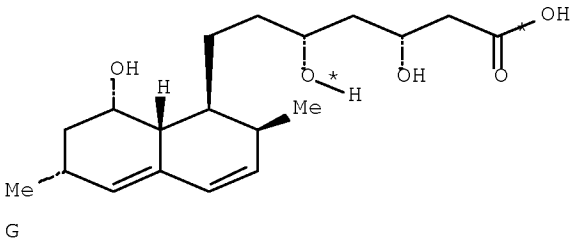


G
YIELD 94%

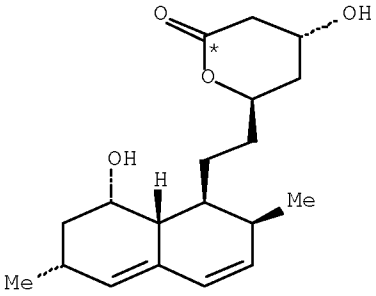
RX(2) RCT F 75330-75-5

RGT H 865-47-4 t-BuOK
PRO G 132748-10-8
SOL 109-99-9 THF

RX(3) OF 15 ...G ===> I...



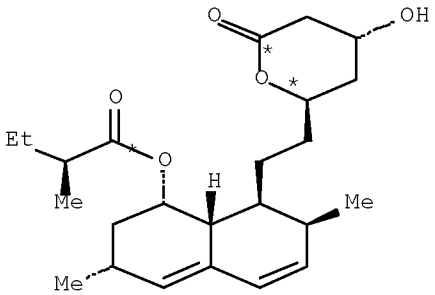
G



I
YIELD 97%

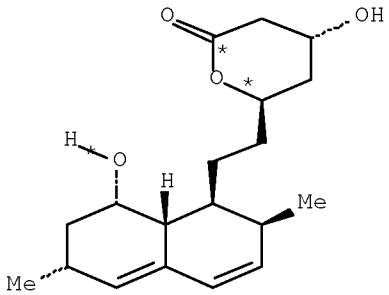
RX(3) RCT G 132748-10-8
RGT J 104-15-4 TsOH
PRO I 79952-42-4
SOL 75-09-2 CH2Cl2

RX(6) OF 15 COMPOSED OF RX(2), RX(3)
RX(6) F ===> I



F

2
STEPS

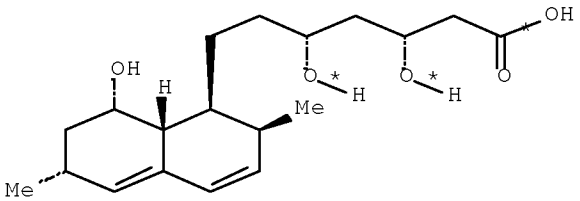


I
YIELD 97%

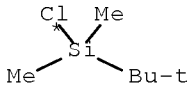
RX(2) RCT F 75330-75-5
RGT H 865-47-4 t-BuOK
PRO G 132748-10-8
SOL 109-99-9 THF

RX(3) RCT G 132748-10-8
RGT J 104-15-4 TsOH
PRO I 79952-42-4
SOL 75-09-2 CH2Cl2

RX(7) OF 15 COMPOSED OF RX(3), RX(4)
RX(7) G + L ===> M

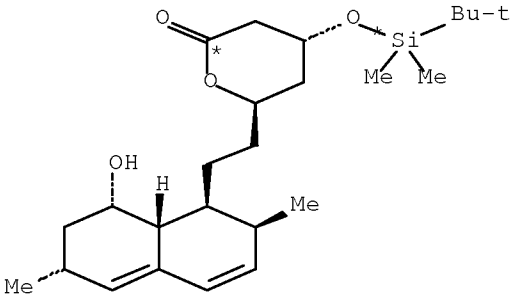


G



L

2
STEPS

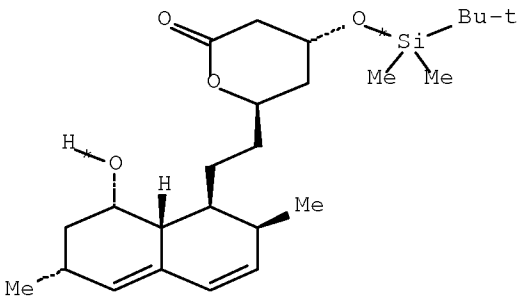


M
YIELD 95%

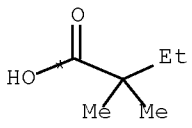
RX(3) RCT G 132748-10-8
RGT J 104-15-4 TsOH
PRO I 79952-42-4
SOL 75-09-2 CH2Cl2

RX(4) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2

RX(9) OF 15 COMPOSED OF RX(5), RX(1)
RX(9) M + O ===> B

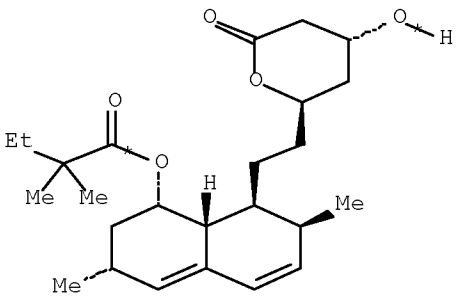


M



O

2
STEPS



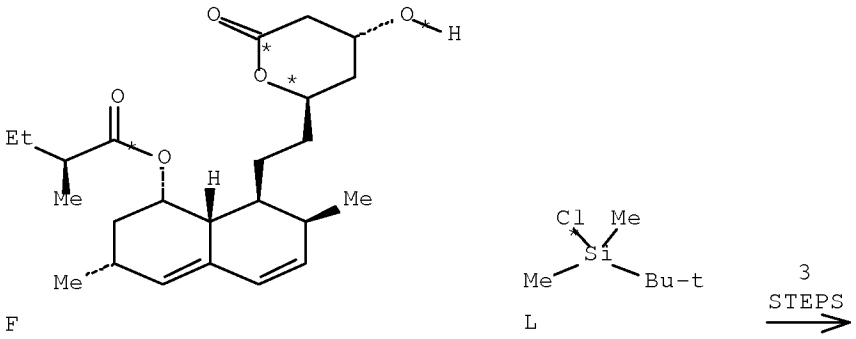
B
YIELD 92%

RX(5) RCT M 79902-31-1, O 595-37-9
RGT P 603-35-0 PPh3, Q 128-08-5 Bromosuccinimide, R 121-69-7 PhNMe2
PRO A 79902-59-3
SOL 75-09-2 CH2Cl2

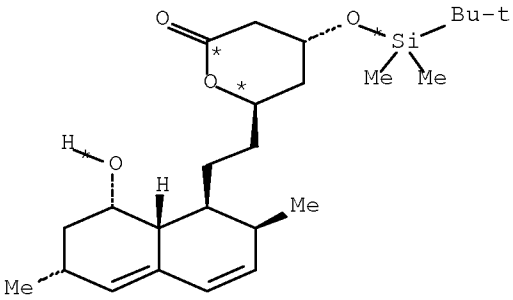
RX(1) RCT A 79902-59-3

RGT C 7647-01-0 HCl
PRO B 79902-63-9
SOL 109-99-9 THF, 123-91-1 Dioxane

RX(10) OF 15 COMPOSED OF RX(2), RX(3), RX(4)
RX(10) F + L ===> M



F L



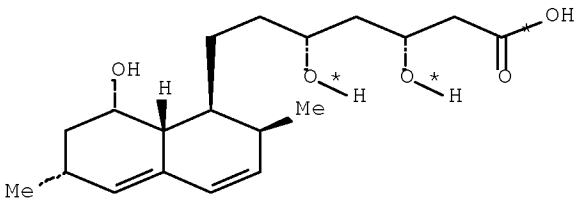
M
YIELD 95%

RX(2) RCT F 75330-75-5
RGT H 865-47-4 t-BuOK
PRO G 132748-10-8
SOL 109-99-9 THF

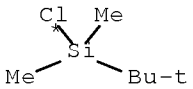
RX(3) RCT G 132748-10-8
RGT J 104-15-4 TsOH
PRO I 79952-42-4
SOL 75-09-2 CH2Cl2

RX(4) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2

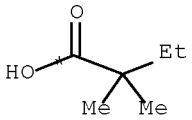
RX(11) OF 15 COMPOSED OF RX(3), RX(4), RX(5)
RX(11) G + L + O ===> A



G

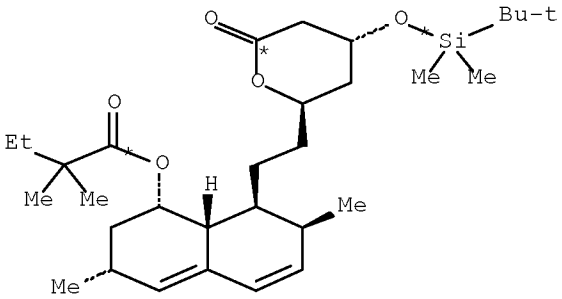


L



O

3
STEPS



A
YIELD 97%

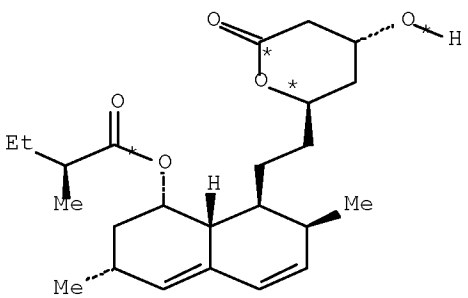
RX(3) RCT G 132748-10-8
RGT J 104-15-4 TsOH
PRO I 79952-42-4
SOL 75-09-2 CH2Cl2

RX(4) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2

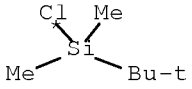
RX(5) RCT M 79902-31-1, O 595-37-9
RGT P 603-35-0 PPh3, Q 128-08-5 Bromosuccinimide, R 121-69-7 PhNMe2
PRO A 79902-59-3
SOL 75-09-2 CH2Cl2

RX(12) OF 15 COMPOSED OF RX(2), RX(3), RX(4), RX(5)

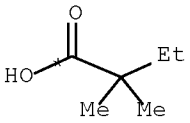
RX(12) F + L + O ===> A



F

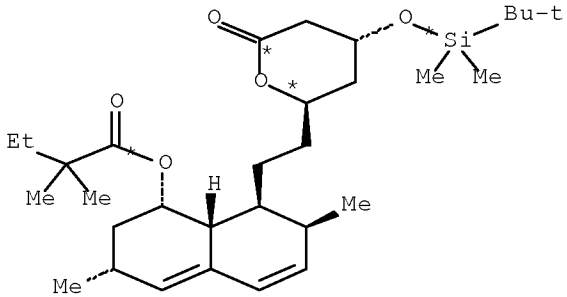


L



O

4
STEPS



A
YIELD 97%

RX(2) RCT F 75330-75-5
RGT H 865-47-4 t-BuOK
PRO G 132748-10-8
SOL 109-99-9 THF

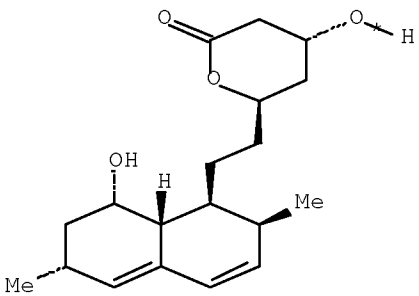
RX(3) RCT G 132748-10-8
RGT J 104-15-4 TsOH
PRO I 79952-42-4
SOL 75-09-2 CH2Cl2

RX(4) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2

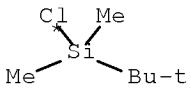
RX(5) RCT M 79902-31-1, O 595-37-9
RGT P 603-35-0 PPh3, Q 128-08-5 Bromosuccinimide, R 121-69-7 PhNMe2
PRO A 79902-59-3
SOL 75-09-2 CH2Cl2

RX(13) OF 15 COMPOSED OF RX(4), RX(5), RX(1)

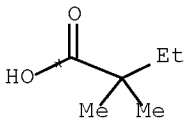
RX(13) I + L + O ===> B



I

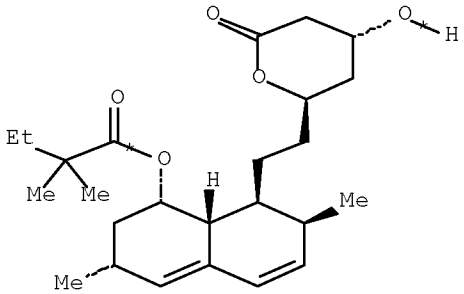


L



O

3 STEPS



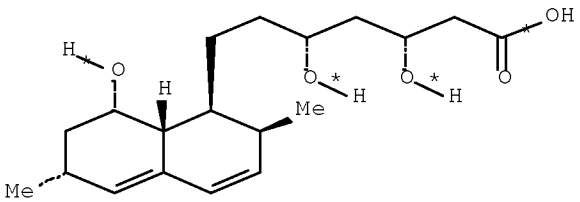
B
YIELD 92%

RX(4) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2

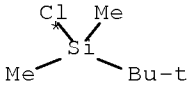
RX(5) RCT M 79902-31-1, O 595-37-9
RGT P 603-35-0 PPh3, Q 128-08-5 Bromosuccinimide, R 121-69-7 PhNMe2
PRO A 79902-59-3
SOL 75-09-2 CH2Cl2

RX(1) RCT A 79902-59-3
RGT C 7647-01-0 HCl
PRO B 79902-63-9
SOL 109-99-9 THF, 123-91-1 Dioxane

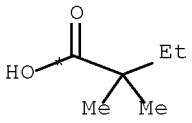
RX(14) OF 15 COMPOSED OF RX(3), RX(4), RX(5), RX(1)
RX(14) G + L + O ===> B



G

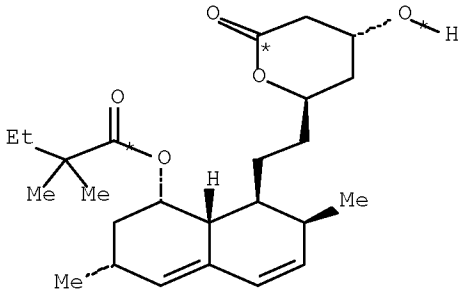


L



O

4
STEPS



B
YIELD 92%

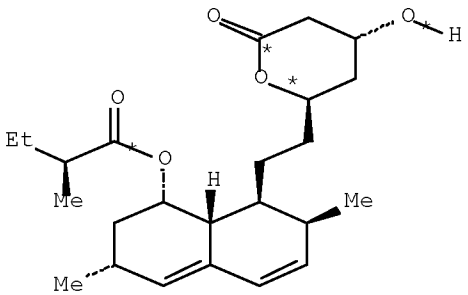
RX(3) RCT G 132748-10-8
RGT J 104-15-4 TsOH
PRO I 79952-42-4
SOL 75-09-2 CH2Cl2

RX(4) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2

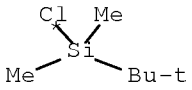
RX(5) RCT M 79902-31-1, O 595-37-9
RGT P 603-35-0 PPh3, Q 128-08-5 Bromosuccinimide, R 121-69-7 PhNMe2
PRO A 79902-59-3
SOL 75-09-2 CH2Cl2

RX(1) RCT A 79902-59-3
RGT C 7647-01-0 HCl
PRO B 79902-63-9
SOL 109-99-9 THF, 123-91-1 Dioxane

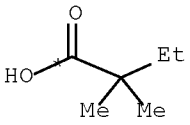
RX(15) OF 15 COMPOSED OF RX(2), RX(3), RX(4), RX(5), RX(1)
RX(15) F + L + O ===> B



F

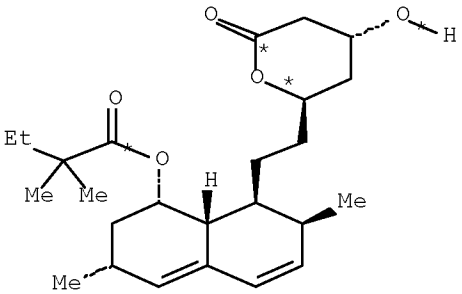


L



O

5
STEPS



B
YIELD 92%

RX(2) RCT F 75330-75-5
RGT H 865-47-4 t-BuOK
PRO G 132748-10-8
SOL 109-99-9 THF

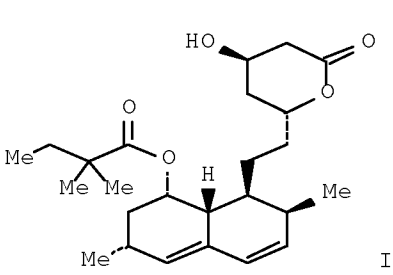
RX(3) RCT G 132748-10-8
RGT J 104-15-4 TsOH
PRO I 79952-42-4
SOL 75-09-2 CH2Cl2

RX(4) RCT I 79952-42-4, L 18162-48-6
RGT N 288-32-4 1H-Imidazole
PRO M 79902-31-1
SOL 75-09-2 CH2Cl2

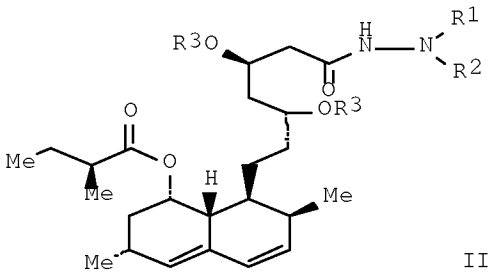
RX(5) RCT M 79902-31-1, O 595-37-9
RGT P 603-35-0 PPh3, Q 128-08-5 Bromosuccinimide, R 121-69-7 PhNMe2
PRO A 79902-59-3
SOL 75-09-2 CH2Cl2

RX(1) RCT A 79902-59-3
RGT C 7647-01-0 HCl
PRO B 79902-63-9
SOL 109-99-9 THF, 123-91-1 Dioxane

```
=> d ibib ed abs hitind hitstr 6-17
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE,
BIOSIS, JAPIO, BIOTECHDS' - CONTINUE? (Y)/N:y



L150 ANSWER 6 OF 29  HCAPLUS  COPYRIGHT 2009 ACS on STN DUPLICATE 4
ACCESSION NUMBER:         2005:696576  HCAPLUS  Full-text
DOCUMENT NUMBER:          143:172683
TITLE:                    A process for the preparation of simvastatin
                          using novel hydrazide intermediates
INVENTOR(S):              Panchasara, Dinesh R.; Jaiswal, Sanjay; Singh, Govind;
                          Bhadwal, Paramvir; Thaper, Rajesh Kumar; Dubey, Sushil
                          Kumar; Khanna, Jag Mohan
PATENT ASSIGNEE(S):       Jubilant Organosys Limited, India
SOURCE:                   PCT Int. Appl., 17 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2005069741         A2    20050804    WO 2004-IN302           20040928
     WO 2005069741         A3    20051222
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
PRIORITY APPLN. INFO.:                       IN 2004-DE108       A  20040121
OTHER SOURCE(S):          CASREACT 143:172683; MARPAT 143:172683
ED   Entered STN:  05 Aug 2005
GI
```



I



II

AB The present invention relates to an industrially feasible process for the preparation of simvastatin (I) using lovastatin hydrazide intermediates, II [R1, R2 = H, alkyl, cycloalkyl, aryl, heteroaryl; R1R2 = cyclyl; R3 = H, hydroxyl protecting group]. The process comprises treating lovastatin or lovastatin ammonium salt with hydrazine or hydrazine derivs., such as R1R2NNH2, to obtain hydrazide intermediates, II [R3 = H (III)], optionally protecting the hydroxyl groups of III to obtain protected lovastatin hydrazide intermediates, II [R3 = hydroxyl protecting group], which is used for the preparation of I. Thus, lovastatin Ph hydrazide, II [R1 = H, R2 = Ph, R3 = H], prepared by the reaction of lovastatin and Ph hydrazine, was reacted with hexamethyldisilazane to provide protected lovastatin Ph hydrazide intermediate II [R1 = H, R2 = Ph, R3 = TMS (IV)]. I was subsequently prepared from IV via methylation with Me iodide, followed by deprotection, hydrolysis and lactonization .

IC ICM C07D

CC 26-6 (Biomolecules and Their Synthetic Analogs)

ST simvastatin prepn lovastatin hydrazide lactonization methylation hydrolysis deprotection

IT Hydrolysis
(acid; during preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

IT Methylation
(during preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

IT Protective groups
(hydroxyl; during preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

IT Asymmetric synthesis and induction
(of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

IT Hydrazides
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for the preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

IT Lactonization
(stereoselective; during preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

IT 64-18-6, Formic acid, uses 64-19-7, Acetic acid, uses 75-75-2, Methanesulfonic acid 76-05-1, Trifluoroacetic acid, uses 98-11-3, Benzenesulfonic acid, uses 104-15-4, p-Toluene sulfonic acid, uses
RL: CAT (Catalyst use); USES (Uses)
(process for the preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

IT 139893-43-9P, Simvastatin ammonium salt 861230-64-0P 861444-60-2P, Lovastatin phenyl hydrazide
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for the preparation of simvastatin from lovastatin or lovastatin ammonium salt using

lovastatin hydrazide intermediates)

IT 79902-63-9P, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for the preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

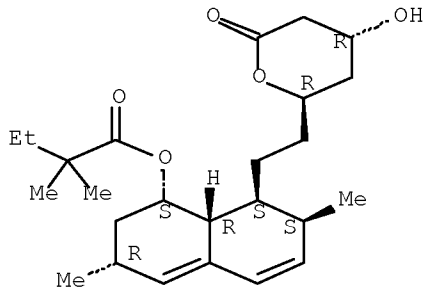
IT 74-83-9, Methyl bromide, reactions 74-88-4, Methyl iodide, reactions 100-63-0, Phenyl hydrazine 999-97-3, Hexamethyldisilazane 75330-75-5, Lovastatin 77550-67-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

IT 79902-63-9P, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for the preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

RN 79902-63-9 HCAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.

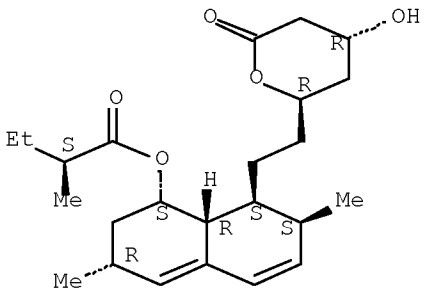


IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of simvastatin from lovastatin or lovastatin ammonium salt using lovastatin hydrazide intermediates)

RN 75330-75-5 HCAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.

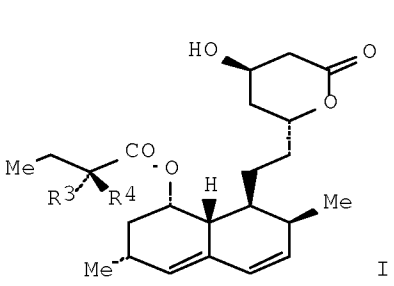


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

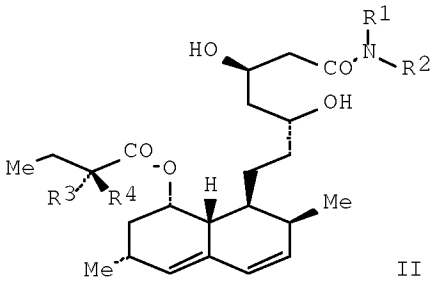
L150 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2005:638861 HCAPLUS Full-text
DOCUMENT NUMBER: 143:133225
TITLE: A novel process for the preparation of simvastatin
INVENTOR(S): Parthasaradhi Reddy, Bandi; Rathnakar Reddy, Kura; Raji Reddy, Rapolu; Muralidhara Reddy, Dasari; Subash Chander Reddy, Kesireddy
PATENT ASSIGNEE(S): Hetero Drugs Limited, India
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005066150	A1	20050721	WO 2004-IN3	20040102
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2004CN00004	A	20051202	IN 2004-CN4	20040102
EP 1699774	A1	20060913	EP 2004-700054	20040102
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK				
US 20060094885	A1	20060504	US 2005-539736	20050620
US 7205415	B2	20070417		

PRIORITY APPLN. INFO.: WO 2004-IN3 W 20040102
OTHER SOURCE(S): CASREACT 143:133225; MARPAT 143:133225
ED Entered STN: 22 Jul 2005
GI



I



II

AB A process for manufacturing simvastatin I (R3 = R4 = Me) was disclosed and comprised the preparation of amide intermediates II [R1 = alkyloxyalkyl, alkylthioalkyl, alkoxyarylalkyl, alkylthioarylalkyl, alkoxycycloalkyl, alkylthiocycloalkyl, etc.] and a subsequent methylation/ lactonization reaction sequence. Thus, lovastatin I (R3 = H, R4 = Me) was reacted with methoxyethylamine to give amide II [R1 = H, R2 = (CH2)2OMe, R3 = H, R4 = Me] which was subsequently alpha methylated on 2-methylbutyryl side chain to form II [R1 = H, R2 = (CH2)2OMe, R3 = R4 = Me] which was in turn hydrolyzed and lactonized to produce simvastatin of high purity.

IC ICM C07D309-30

CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 63

ST simvastatin prepn amide intermediate amidation lactonization

IT Amidation
Lactonization
(process for the preparation of simvastatin)

IT 75225-51-3P 77550-67-5P 101314-97-0P 151006-17-6P 858924-46-6P 858924-52-4P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(claimed intermediate; process for the preparation of simvastatin)

IT 139893-43-9P, Simvastatin ammonium salt 858924-14-8P 858924-20-6P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for the preparation of simvastatin)

IT 79902-63-9P, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the preparation of simvastatin)

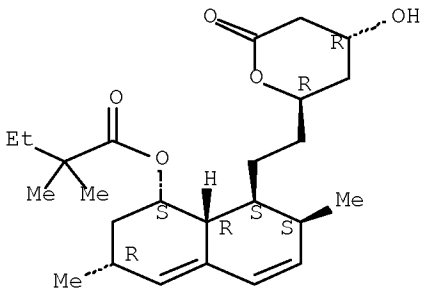
IT 109-85-3 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of simvastatin)

IT 79902-63-9P, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the preparation of simvastatin)

RN 79902-63-9 HCAPLUS

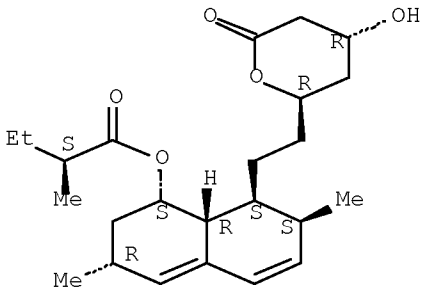
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of simvastatin)
RN 75330-75-5 HCAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



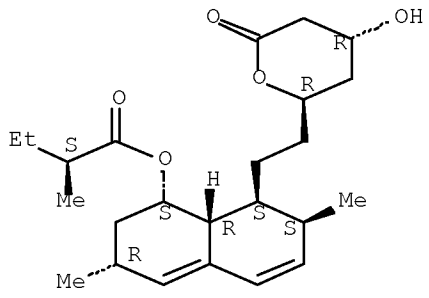
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L150 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:927672 HCAPLUS Full-text
DOCUMENT NUMBER: 150:447713
TITLE: A process for preparation of simvastatin
INVENTOR(S): Shah, Niraj Shyamlal; Dwivedi, Shriprakash Dhar
PATENT ASSIGNEE(S): Cadila Healthcare Limited, India
SOURCE: Indian Pat. Appl., 34pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2006MU01100	A	20080725	IN 2006-MU1100	20060711

PRIORITY APPLN. INFO.: IN 2006-MU1100 20060711
ED Entered STN: 05 Aug 2008
AB A process for the preparation of simvastatin is disclosed. The process is demonstrated by preparing simvastatin by lactonization of simvastatin acid ammonium salt. A key advantage to the process is the ability to produce simvastatin with high purity using a simple and safe procedure that can be employed for com. production
IC ICM C07D309-30
CC 27-13 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 63
ST simvastatin prepn lactonization; ammonia simvastatin salt lactonization
IT Lactonization
(a process for preparation of simvastatin via lactonization of simvastatin acid ammonium salt)
IT Acids, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(organic; a process for preparation of simvastatin via lactonization of simvastatin acid ammonium salt)
IT 109-73-9, 1-Butanamine, reactions 75330-75-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(a process for preparation of simvastatin via lactonization of simvastatin acid ammonium salt)
IT 134970-30-2P 134970-31-3P 139893-43-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(a process for preparation of simvastatin via lactonization of simvastatin acid ammonium salt)
IT 79902-63-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(a process for preparation of simvastatin via lactonization of simvastatin acid ammonium salt)
IT 75330-75-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(a process for preparation of simvastatin via lactonization of simvastatin acid ammonium salt)
RN 75330-75-5 HCAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



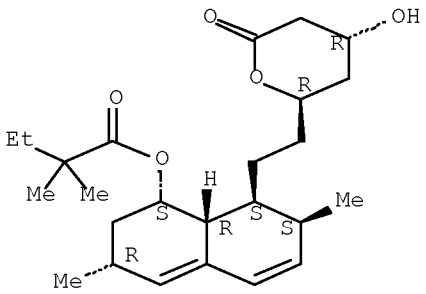
IT 79902-63-9P
RL: SPN (Synthetic preparation); PREP (Preparation)

(a process for preparation of simvastatin via lactonization of simvastatin acid ammonium salt)

RN 79902-63-9 HCAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



L150 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:848858 HCAPLUS Full-text

DOCUMENT NUMBER: 150:398359

TITLE: Process for preparation of Simvastatin from lactonization of Simvastatin acid and derivatives

INVENTOR(S): Shah, Niraj Shyamlal; Dwivedi, Shriprakash Dhar; Lohray, Vidya Bhushan; Lohray, Braj Bhushan

PATENT ASSIGNEE(S): Cadila Healthcare Limited, India

SOURCE: Indian Pat. Appl., 34pp.
CODEN: INXXBQ

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2006MU00861	A	20080704	IN 2006-MU861	20060605

PRIORITY APPLN. INFO.: IN 2006-MU861 20060605

OTHER SOURCE(S): CASREACT 150:398359

ED Entered STN: 15 Jul 2008

AB This invention provides an improved process of for preparing highly pure Simvastatin comprising lactonization of Simvastatin acid and derivs. For example, Simvastatin acid ammonium salt was reacted in acetonitrile at 25-35 °C for 18 h in the presence of citric acid to give Simvastatin. The crude Simvastatin can be optionally purified with suitable organic solvent.

IC ICM C07D309-30

CC 27-13 (Heterocyclic Compounds (One Hetero Atom))

ST prepn Simvastatin lactonization high purity

IT Acids, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(organic; preparation of Simvastatin from lactonization of Simvastatin acid and derivs.)

IT Lactonization

(preparation of Simvastatin from lactonization of Simvastatin acid and derivs.)

IT 109-73-9, 1-Butanamine, reactions 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Simvastatin from lactonization of Simvastatin acid and derivs.)

IT 121009-77-6P, Simvastatin acid 134970-30-2P 134970-31-3P
139893-43-9P, Simvastatin ammonium salt
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Simvastatin from lactonization of Simvastatin acid and derivs.)

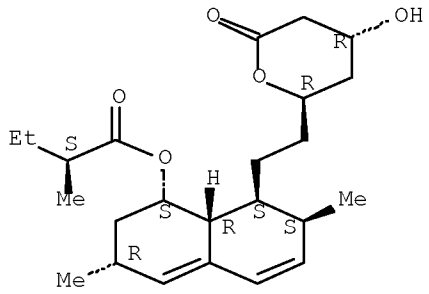
IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of Simvastatin from lactonization of Simvastatin acid and derivs.)

IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Simvastatin from lactonization of Simvastatin acid and derivs.)

RN 75330-75-5 HCAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.

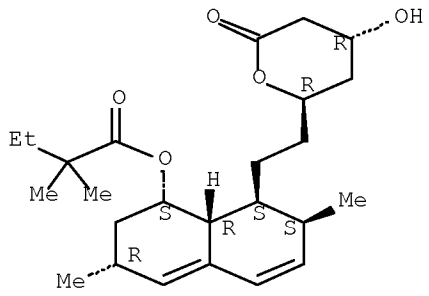


IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of Simvastatin from lactonization of Simvastatin acid and derivs.)

RN 79902-63-9 HCAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



L150 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:686298 HCAPLUS Full-text
DOCUMENT NUMBER: 149:79402
TITLE: Process for synthesis of Simvastatin
INVENTOR(S): Ma, Qunli; Ma, Jianyong
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 101190907	A	20080604	CN 2006-10149097	20061124

PRIORITY APPLN. INFO.: CN 2006-10149097 20061124
OTHER SOURCE(S): CASREACT 149:79402
ED Entered STN: 09 Jun 2008
AB This invention relates to a process for the preparation of Simvastatin . For example, tert-butyldimethylsilyl protected Lovastatin butylamide was methylated using chloromethane in the presence of LiBu/pyrrolidine, followed by deprotection with 4-methylbenzenesulfonic acid and hydrolysis in the presence of sodium hydroxide to obtain Simvastatin acid. Simvastatin acid obtained in the previous step was dehydrated to give Simvastatin. The process can be used for methylation of other Vastatin drugs and products.
CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 45
ST prepn Simvastatin methylation lactonization
IT Hydrolysis
Lactonization
Methylation
(preparation of Simvastatin)
IT Acids, uses
RL: CAT (Catalyst use); USES (Uses)
(preparation of Simvastatin)
IT Bases, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of Simvastatin)
IT Amines, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(secondary; preparation of Simvastatin)
IT 121009-77-6P, Simvastatin acid 134970-31-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic

preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Simvastatin)

IT 79902-63-9P, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of Simvastatin)

IT 74-87-3, Chloromethane, reactions 109-73-9, 1-Butanamine, reactions 18162-48-6, tert-Butyldimethylchlorosilane 75330-75-5, Lovastatin 134970-30-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Simvastatin)

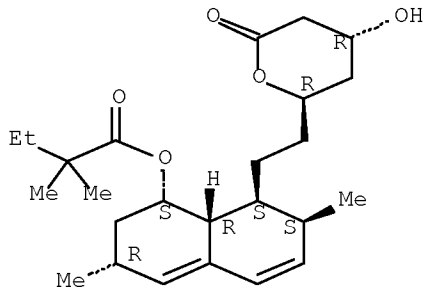
IT 7439-93-2D, Lithium, alkyl compds.
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of Simvastatin)

IT 79902-63-9P, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of Simvastatin)

RN 79902-63-9 HCAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.

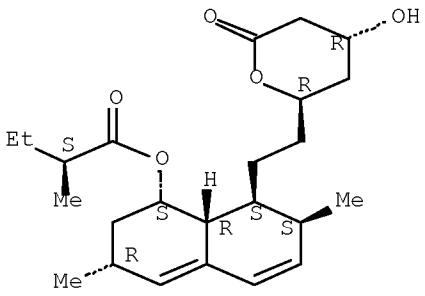


IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Simvastatin)

RN 75330-75-5 HCAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

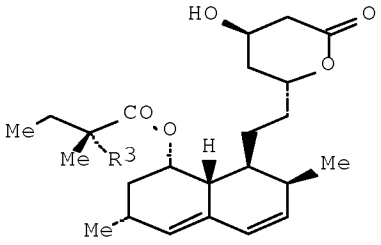
Absolute stereochemistry.



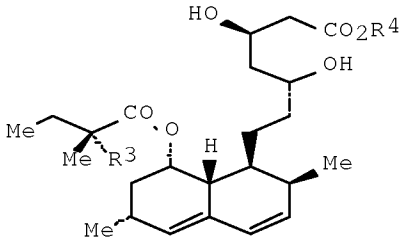
L150 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1155550 HCAPLUS Full-text
DOCUMENT NUMBER: 143:422203
TITLE: Processes for the preparation of simvastatin
INVENTOR(S): Joshi, Narendra Shriram; Bhirud, Shekhar Bhaskar; Rao, Kodali Eswara
PATENT ASSIGNEE(S): Glenmark Pharmaceuticals Limited, India
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20050239885	A1	20051027	US 2005-112893		20050422
IN 2004MU00480	A	20060616	IN 2004-MU480		20040423
PRIORITY APPLN. INFO.:			US 2004-564420P	P	20040422
			IN 2004-MU480	T0	20040423

OTHER SOURCE(S): CASREACT 143:422203; MARPAT 143:422203
ED Entered STN: 28 Oct 2005
GI



I



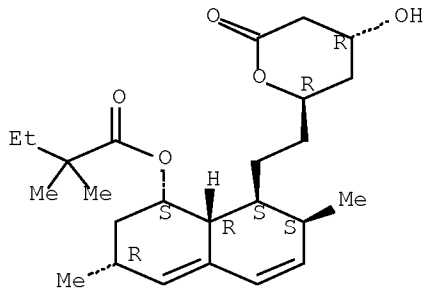
II

AB Improved processes were disclosed for the preparation of simvastatin I (R3 = Me), a 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) inhibitor, via lactonization of simvastatin ammonium salt II (R3 = Me, R4 = H.NH3). This process comprised. reacting lovastatin I (R = H) with an amine HNR1R2 (R1, R2 = H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, etc.) in an aqueous medium to provide a corresponding carboxylic acid amine salt II (R = H, R4 =

H.HNR1R2), methylation of the resulting lovastatin salt using a base, such as tert-BuLi, to form the corresponding simvastatin amine salt II (R = Me, R4 = H.HNR1R2), conversion of the simvastatin amine salt to simvastatin ammonium salt II (R3 = Me, R4 = H.NH3), and finally, lactonization of the simvastatin ammonium salt to for the desired simvastatin with purity >99%.

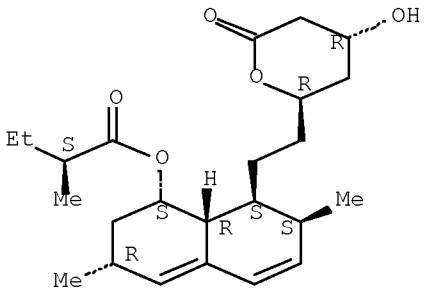
IC ICM A61K031-225
ICS C07C067-02
INCL 514548000; X56-025.6
CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 63
ST simvastatin prepn purifn lactonization
IT Lactonization
(processes for preparation and purification of simvastatin via a lactonization reaction of simvastatin ammonium salts)
IT 79902-63-9P, Simvastatin
RL: PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(processes for preparation and purification of simvastatin via a lactonization reaction of simvastatin ammonium salts)
IT 75-64-9, tert-Butylamine, reactions 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(processes for preparation and purification of simvastatin via a lactonization reaction of simvastatin ammonium salts)
IT 139893-43-9P, Simvastatin Ammonium Salt 262285-81-4P, Lovastatin tert-butylamine Salt 262291-01-0P, Simvastatin tert-butylamine salt
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(processes for preparation and purification of simvastatin via a lactonization reaction of simvastatin ammonium salts)
IT 79902-63-9P, Simvastatin
RL: PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(processes for preparation and purification of simvastatin via a lactonization reaction of simvastatin ammonium salts)
RN 79902-63-9 HCAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(processes for preparation and purification of simvastatin via a lactonization reaction of simvastatin ammonium salts)
RN 75330-75-5 HCAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



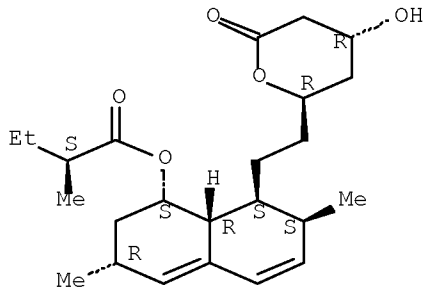
L150 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1189249 HCAPLUS Full-text
DOCUMENT NUMBER: 143:440154
TITLE: Novel method for synthesis of Simvastatin
INVENTOR(S): Dai, Haiyan; Song, Aigang; Chen, Sheng; Yu, Chuanjun; Zhang, Dongmei; Cai, Yahui
PATENT ASSIGNEE(S): Shandong Lukang Pharmaceutical Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 13 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1583737	A	20050223	CN 2004-10024320	20040609
CN 1255398	C	20060510		

PRIORITY APPLN. INFO.: CN 2004-10024320 20040609
OTHER SOURCE(S): CASREACT 143:440154
ED Entered STN: 09 Nov 2005
AB The invention relates to a novel, convenient and effective method for synthesis Simvastatin via methylation route. In this procedure, a new protective agent bis(trialkylsilyl)urea is adopted to protect the hydroxyl group in the absence of any catalyst (such as imidazole). When bis(trimethylsilyl)urea is used as the protective agent, it comes off automatically by hydrolysis after methylation, which results in simplified process and reduced cost. High quality Simvastatin can be obtained from Simvastatin acid by direct spray-drying and ring-closure lactonization. The invention also provides a method for purifying Simvastatin by absorbing the trace impurities (such as dimmer).
IC ICM C07D309-30

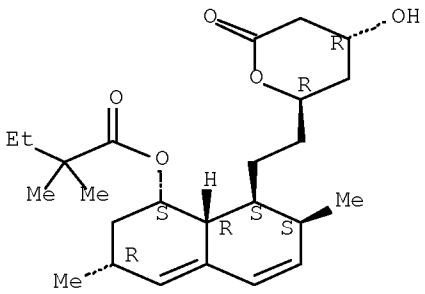
CC 26-6 (Biomolecules and Their Synthetic Analogs)
ST Simvastatin synthesis Lovastatin methylation lactonization
IT Lactonization
Methylation
(synthesis of Simvastatin)
IT 74-88-4, Methyl iodide, reactions 109-73-9, n-Butylamine, reactions 18297-63-7, Bis(trimethylsilyl)urea 55526-39-1 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of Simvastatin)
IT 134970-29-9P 134970-33-5P 405225-86-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of Simvastatin)
IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of Simvastatin)
IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of Simvastatin)
RN 75330-75-5 HCAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of Simvastatin)
RN 79902-63-9 HCAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

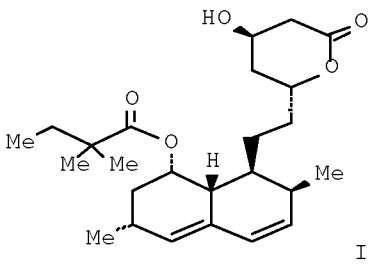
Absolute stereochemistry.



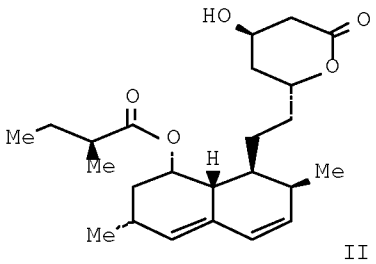
L150 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:718829 HCAPLUS Full-text
DOCUMENT NUMBER: 147:343856
TITLE: Method for obtaining simvastatin from lovastatin.
INVENTOR(S): Galeazzi Toscani, Edvige
PATENT ASSIGNEE(S): Fermic, S.A. de C.V., Mex.
SOURCE: Mex. Pat. Appl., 17pp.
CODEN: MXXXA3
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
MX 2001010721	A	20030428	MX 2001-10721	20011023

PRIORITY APPLN. INFO.: MX 2001-10721 20011023
OTHER SOURCE(S): CASREACT 147:343856
ED Entered STN: 03 Jul 2007
GI



I



II

AB The present invention refers to a method for obtaining simvastatin (I) from lovastatin (II). The method comprises alkylation of alpha carbon of the secondary chain 2-methylbutyrate of the lovastatin for obtaining simvastatin with high yields and enhanced purity. Thus, I was prepared from II via amidation/lactone cleavage with BuNH2, silylation with (Me3Si)2NH in DMF, alkylation with MeI in THF containing lithium pyrrolidide, saponification with

NaOH in MeOH, salt formation with NH2OH in MeOH, and lactonization with HCl in CH2Cl2.

IC ICM C07D309-30
CC 26-6 (Biomolecules and Their Synthetic Analogs)
ST simvastatin prepn; lovastatin deriv alkylation; methylbutyrate secondary chain alkylation
IT Methylation
(of lovastatin amide disilyl ether; method for obtaining simvastatin from lovastatin.)
IT Amidation
(of lovastatin with butylamine; method for obtaining simvastatin from lovastatin.)
IT Lactonization
(of simvastatin acid ammonium salt; method for obtaining simvastatin from lovastatin.)
IT Hydrolysis
(of simvastatin amide; method for obtaining simvastatin from lovastatin.)
IT Precipitation (chemical)
(of simvastatin with ammonium hydroxide; method for obtaining simvastatin from lovastatin.)
IT Crystallization
(of simvastatin; method for obtaining simvastatin from lovastatin.)
IT Alkylation
(regioselective; method for obtaining simvastatin from lovastatin.)
IT Natural products
(statins; method for obtaining simvastatin from lovastatin.)
IT 7727-37-9, Nitrogen, uses
RL: NUU (Other use, unclassified); USES (Uses)
(alkylation atmospheric; method for obtaining simvastatin from lovastatin.)
IT 74-88-4, Methyl iodide, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of lovastatin derivative; method for obtaining simvastatin from lovastatin.)
IT 109-99-9, THF, uses
RL: NUU (Other use, unclassified); USES (Uses)
(alkylation solvent; method for obtaining simvastatin from lovastatin.)
IT 109-73-9, Butylamine, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(amidation by, of lovastatin; method for obtaining simvastatin from lovastatin.)
IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(amidation of, with butylamine; method for obtaining simvastatin from lovastatin.)
IT 7440-44-0D, Carbon, activated
RL: RGT (Reagent); RACT (Reactant or reagent)
(crystallization agent; method for obtaining simvastatin from lovastatin.)
IT 64-17-5, Ethanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(crystallization solvent; method for obtaining simvastatin from lovastatin.)
IT 21369-64-2, Hexyllithium
RL: RGT (Reagent); RACT (Reactant or reagent)

(deprotonation by, of pyrrolidine; method for obtaining simvastatin from lovastatin.)

IT 67-56-1, Methanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(hydrolyis and precipitation solvent; method for obtaining simvastatin from lovastatin.)

IT 1310-73-2, Sodium hydroxide, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(hydrolysis agent; method for obtaining simvastatin from lovastatin.)

IT 75-09-2, Methylene chloride, uses
RL: NUU (Other use, unclassified); USES (Uses)
(lactonization solvent; method for obtaining simvastatin from lovastatin.)

IT 123-75-1, Pyrrolidine, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(lithiation and deprotonation by, of lovastatin amide derivative; method for obtaining simvastatin from lovastatin.)

IT 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(method for obtaining simvastatin from lovastatin.)

IT 121009-77-6P, Simvastatin acid 134970-33-5P 139893-43-9P, Simvastatin acid ammonium salt
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(method for obtaining simvastatin from lovastatin.)

IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); PREP (Preparation)
(method for obtaining simvastatin from lovastatin.)

IT 1336-21-6, Ammonium hydroxide
RL: RGT (Reagent); RACT (Reactant or reagent)
(precipitation agent; method for obtaining simvastatin from lovastatin.)

IT 4439-90-1P, Lithium pyrrolidide
RL: RGT (Reagent); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deprotonation by, of lovastatin amide derivative; method for obtaining simvastatin from lovastatin.)

IT 473723-78-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and regioselective methylation of; method for obtaining simvastatin from lovastatin.)

IT 134970-29-9P, Lovastatin butyl amide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and silylation of; method for obtaining simvastatin from lovastatin.)

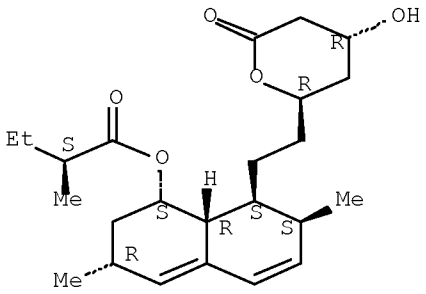
IT 7647-01-0, Hydrochloric acid, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(reaction quencher; method for obtaining simvastatin from lovastatin.)

IT 999-97-3, Hexamethyldisilazane
RL: RCT (Reactant); RACT (Reactant or reagent)
(silylation by, of lovastatin amide; method for obtaining simvastatin from lovastatin.)

IT 68-12-2, Dimethylformamide, uses
RL: NUU (Other use, unclassified); USES (Uses)
(silylation solvent; method for obtaining simvastatin from lovastatin.)

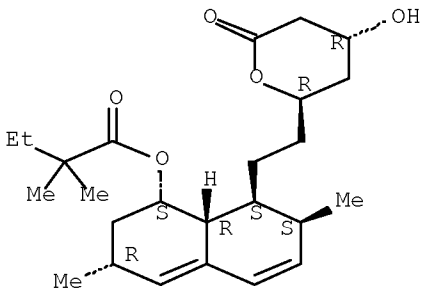
IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(amidation of, with butylamine; method for obtaining simvastatin from lovastatin.)
RN 75330-75-5 HCAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); PREP (Preparation)
(method for obtaining simvastatin from lovastatin.)
RN 79902-63-9 HCAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



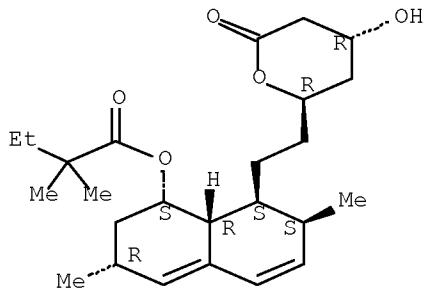
L150 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:955975 HCAPLUS Full-text
DOCUMENT NUMBER: 142:197752
TITLE: Method of preparation of simvastatin and intermediates thereof
INVENTOR(S): Kim, Sang Rin; Kim, Ji Han; Lee, Jae Seung; Lee, Yong Taek; Lee, Seung Ho
PATENT ASSIGNEE(S): Boryung Pharmaceutical Co., Ltd., S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, No pp. given

CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2003077183	A	20031001	KR 2002-16129	20020325

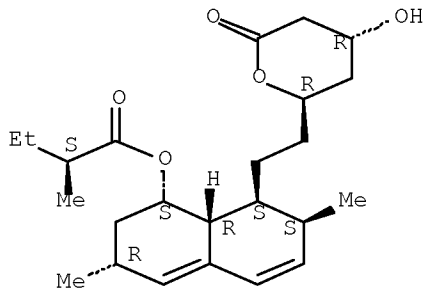
PRIORITY APPLN. INFO.: KR 2002-16129 20020325
ED Entered STN: 10 Nov 2004
AB Provided is a method for preparing simvastatin and intermediates thereof which uses lovastatin as a starting material, and performs deacylation, lactonization and acylation to make an antihyperlipidemic agent. The method of preparing the simvastatin expressed by formula 1 comprises the step of forming intermediate compound expressed by formula 3 by making deacylation with respect to the compound expressed by formula 2 with a mixed solvent of aprotic polar solvent and water, or metal hydroxide. The aprotic polar solvent is selected from the group consisting of DMSO, DMF, N-Me pyrrolidine, or hexamethyl phosphoramide. The metal hydroxide is selected from the group consisting of lithium hydroxide, sodium hydroxide, and potassium hydroxide.
IC ICM C07D309-30
CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1
ST simvastatin prepn deacylation lactonization acylation antihyperlipidemic agent
IT Acylation
Deacylation
Hypolipemic agents
Lactonization
(preparation of simvastatin and intermediates thereof)
IT 79902-63-9P, Simvastatin
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of simvastatin and intermediates thereof)
IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of simvastatin and intermediates thereof)
IT 79902-63-9P, Simvastatin
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of simvastatin and intermediates thereof)
RN 79902-63-9 HCAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of simvastatin and intermediates thereof)
RN 75330-75-5 HCAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



L150 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:906186 HCAPLUS Full-text
DOCUMENT NUMBER: 138:4469
TITLE: Preparation of simvastatin from simvastatin acid derivatives via lactonization in an organic solvent
INVENTOR(S): Ramesh, Dandala; Sonny, Sebastian; Sanapureddy, Jagan Mohan Reddy; Meenakshisunderam, Sivakumaran
PATENT ASSIGNEE(S): Aurobindo Pharma Limited, India
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002094804	A1	20021128	WO 2002-IN122	20020516

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, TM

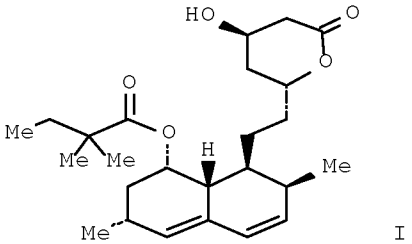
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IN 193614	A1	20040724	IN 2001-MA401		20010518
AU 2002319892	A1	20021203	AU 2002-319892		20020516
EP 1294706	A1	20030326	EP 2002-749274		20020516
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
SI 21235	A	20031231	SI 2002-20005		20020516
JP 2004520445	T	20040708	JP 2002-591477		20020516
BG 107475	A	20040130	BG 2003-107475		20030117
US 20040019225	A1	20040129	US 2003-440537		20030519
US 6797831	B2	20040928			
PRIORITY APPLN. INFO.:			IN 2001-MA401	A	20010518
			WO 2002-IN122	W	20020516

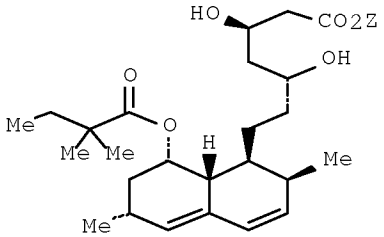
OTHER SOURCE(S): CASREACT 138:4469

ED Entered STN: 29 Nov 2002

GI



I



II

AB The present invention discloses a process for preparation of simvastatin (I) from simvastatin acid derivs., such as II [Z = H, NH4], via heating in an organic solvent selected from xylenes, ethylbenzene and mixts. thereof. Thus, II [Z = NH4] (also prepared) was added to xylenes and the reaction mixture was refluxed at 130 to 140 °C with constant nitrogen purging for 30 min to afford I (yield = >94.8 %).

IC ICM C07D309-30

CC 26-6 (Biomolecules and Their Synthetic Analogs)

ST simvastatin prepn; lactonization simvastatin acid deriv org solvent

IT Heating
(of simvastatin acid derivs. in an organic solvent in preparation of simvastatin)

IT Solvents
(organic; preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)

IT Lactonization
(stereoselective; of simvastatin acid derivs. in an organic solvent in preparation of simvastatin)

IT 476305-24-5P
RL: BYP (Byproduct); PREP (Preparation)

(preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)

IT 139893-43-9P, Simvastatin acid ammonium salt 476305-25-6P 476305-26-7P 476468-68-5P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)

IT 79902-63-9P, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)

IT 100-41-4, Ethylbenzene, uses 1330-20-7, Xylene, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)

IT 74-88-4, Methyl iodide, reactions 100-46-9, Benzylamine, reactions 75330-75-5, Lovastatin 121009-77-6, Simvastatin acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)

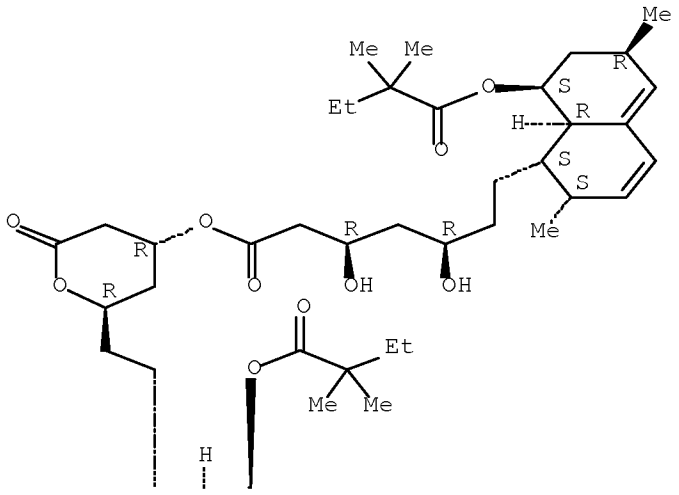
IT 476305-24-5P
RL: BYP (Byproduct); PREP (Preparation)
(preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)

RN 476305-24-5 HCAPLUS

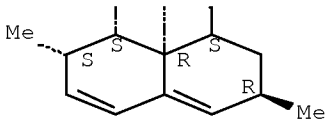
CN 1-Naphthaleneheptanoic acid, 8-(2,2-dimethyl-1-oxobutoxy)-1,2,6,7,8,8a-hexahydro-β,δ-dihydroxy-2,6-dimethyl-, (2R,4R)-2-[2-[(1S,2S,6R,8S,8aR)-8-(2,2-dimethyl-1-oxobutoxy)-1,2,6,7,8,8a-hexahydro-2,6-dimethyl-1-naphthalenyl]ethyl]tetrahydro-6-oxo-2H-pyran-4-yl ester, (βR,δR,1S,2S,6R,8S,8aR)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

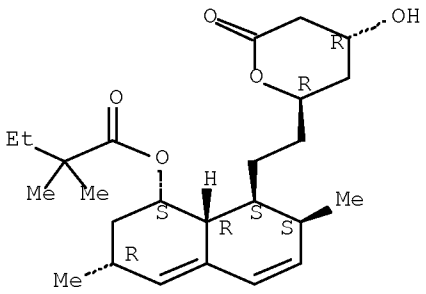


PAGE 2-A



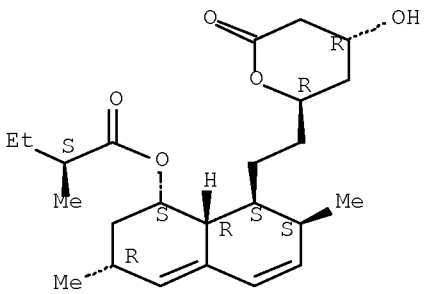
IT 79902-63-9P, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)
RN 79902-63-9 HCAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of simvastatin from simvastatin acid derivs. via lactonization in an organic solvent)
RN 75330-75-5 HCAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.

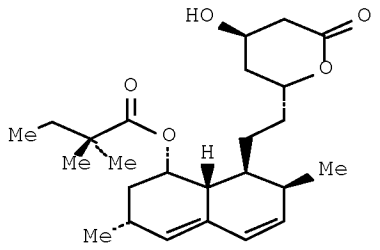


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L150 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:107100 HCAPLUS Full-text
DOCUMENT NUMBER: 136:167217
TITLE: Highly purified simvastatin compositions
INVENTOR(S): Csaba, Szabo; Ferenc, Korodi; Istvan, Melczer; Szabolcs, Salyi; Leonov, David
PATENT ASSIGNEE(S): Teva Pharmaceuticals Industries, Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009697	A1	20020207	WO 2001-US23525	20010726
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2419206	A1	20020207	CA 2001-2419206	20010726
US 20020115712	A1	20020822	US 2001-916662	20010726
US 6686481	B2	20040203		
EP 1303268	A1	20030423	EP 2001-961736	20010726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 2003002963	A2	20031229	HU 2003-2963	20010726
HU 2003002963	A3	20040301		
JP 2004505045	T	20040219	JP 2002-515250	20010726
AU 2001282981	B2	20040805	AU 2001-282981	20010726
NZ 524418	A	20041224	NZ 2001-524418	20010726
RU 2275909	C2	20060510	RU 2003-105219	20010726
IN 2003MN00031	A	20050204	IN 2003-MN31	20030106
ZA 2003000344	A	20040121	ZA 2003-344	20030113
MX 2003000748	A	20040625	MX 2003-748	20030124
KR 542094	B1	20060111	KR 2003-701063	20030124
PRIORITY APPLN. INFO.:			US 2000-221112P P	20000727
			WO 2001-US23525 W	20010726

OTHER SOURCE(S): CASREACT 136:167217
ED Entered STN: 10 Feb 2002
GI



I

AB The present invention relates to a process to prepare semi synthetic statins, to intermediates formed during said process and to highly purified simvastatin (I) produced by the process.

IC ICM A61K031-34
ICS C07D309-30

CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 63

ST purified simvastatin prepn lactone ring opening amidation lovastatin; deacylation lactone ring formation simvastatin ammonium salt lactonization acylation

IT Ring opening
(lactone; preparation of highly purified simvastatin via)

IT Asymmetric synthesis and induction
(preparation of highly purified simvastatin)

IT Acylation
Amidation
Deacylation
Lactonization
(preparation of highly purified simvastatin via)

IT 79902-63-9P
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of highly purified simvastatin)

IT 98-88-4, Benzoyl chloride 108-91-8, Cyclohexylamine, reactions 109-73-9, n-Butylamine, reactions 110-89-4, Piperidine, reactions 111-68-2, Heptylamine 123-75-1, Pyrrolidine, reactions 5856-77-9, 2,2-Dimethylbutyryl chloride 75330-75-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of highly purified simvastatin)

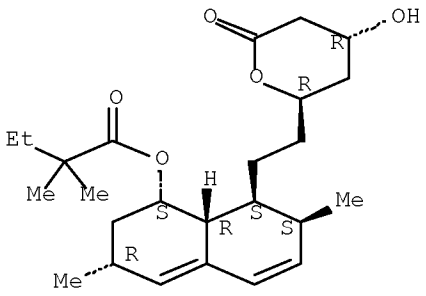
IT 134970-29-9P 134970-30-2P 134970-31-3P 136432-10-5P 136432-11-6P 139893-43-9P 163448-20-2P 210980-52-2P 210980-53-3P 210980-54-4P 210980-56-6P 210980-60-2P 210980-62-4P 210980-69-1P 396712-34-8P 396712-35-9P 396712-36-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of highly purified simvastatin)

IT 79902-63-9P
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of highly purified simvastatin)

RN 79902-63-9 HCAPLUS

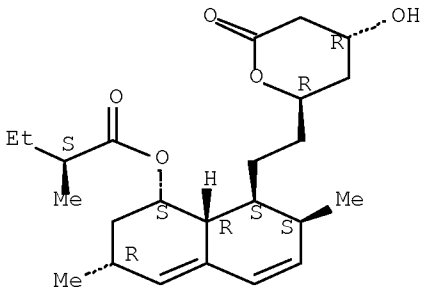
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



IT 75330-75-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of highly purified simvastatin)
RN 75330-75-5 HCAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



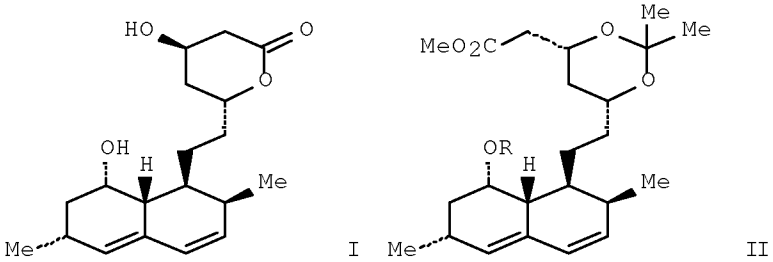
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L150 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:401812 HCAPLUS Full-text
DOCUMENT NUMBER: 133:17379
TITLE: Process for producing simvastatin from lovastatin
INVENTOR(S): Taoka, Naoaki; Inoue, Kenji
PATENT ASSIGNEE(S): Kaneka Corporation, Japan
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000034264	A1	20000615	WO 1999-JP6929	19991210
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320163	A1	20000615	CA 1999-2320163	19991210
CA 2320163	C	20080923		
EP 1055671	A1	20001129	EP 1999-959738	19991210
EP 1055671	B1	20041201		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
SI 20327	A	20010228	SI 1999-20024	19991210
HU 2001003021	A2	20011228	HU 2001-3021	19991210
HU 2001003021	A3	20020429		
CN 1122029	C	20030924	CN 1999-802754	19991210
CN 1493570	A	20040505	CN 2003-2003153045	19991210
CN 1226296	C	20051109		
AT 283849	T	20041215	AT 1999-959738	19991210
EP 1533308	A2	20050525	EP 2004-23298	19991210
EP 1533308	A3	20050914		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
ES 2234323	T3	20050616	ES 1999-959738	19991210
CZ 299522	B6	20080827	CZ 2000-3149	19991210
CZ 299566	B6	20080903	CZ 2008-99	19991210
MX 2000007791	A	20020225	MX 2000-7791	20000809
US 6331641	B1	20011218	US 2000-601794	20000928
PRIORITY APPLN. INFO.:			JP 1998-351865 A	19981210
			EP 1999-959738 A3	19991210
			WO 1999-JP6929 W	19991210

OTHER SOURCE(S): CASREACT 133:17379; MARPAT 133:17379
ED Entered STN: 16 Jun 2000
GI



AB A convenient, efficient and industrially favorable process for producing simvastatin, which is useful as an HMG-coA reductase inhibitor (no data), is described. This process comprises deacylating lovastatin by treating with an inorg. base and a secondary or tertiary alc. to thereby form diol lactone, and then selectively protecting, acylating, deblocking, and lactonizing the diol

lactone by using a ketal or acetal protective group to thereby give simvastatin. Thus, saponification of lovastatin with KOH in tert-Bu alc. at room temperature for 30 min and then under reflux for 4 h followed by acidification with H3PO4 and treatment with MeSO3H in iso-Pr acetate gave diol lactone (I) which underwent ketalization with 2,2-dimethoxypropane in the presence of p-MeC6H4SO3H in CH2Cl2 at room temperature for 1 h to give acetonide (II; R = H). Acylation of the latter alc. with 2,2-dimethylbutyryl chloride in the presence of 4-dimethylaminopyridine in pyridine at 100° for 6 h gave II (R = MeCH2CMe2CO) which was treated with aqueous 1 N HCl in MeCN at room temperature for 4 h to give simvastatin.

IC ICM C07D309-30
ICS C07D319-06

CC 27-13 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 7

ST simvastatin prepn HMG coA reductase inhibitor

IT 9028-35-7, HMG-CoA reductase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(process for producing simvastatin from lovastatin)

IT 77-76-9, 2,2-Dimethoxypropane 5856-77-9, 2,2-Dimethylbutyryl chloride 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for producing simvastatin from lovastatin)

IT 79952-42-4P 132748-10-8P 272456-96-9P 272456-97-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for producing simvastatin from lovastatin)

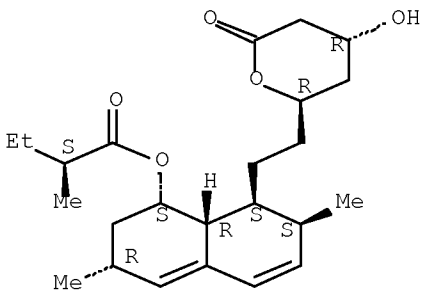
IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for producing simvastatin from lovastatin)

IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for producing simvastatin from lovastatin)

RN 75330-75-5 HCAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

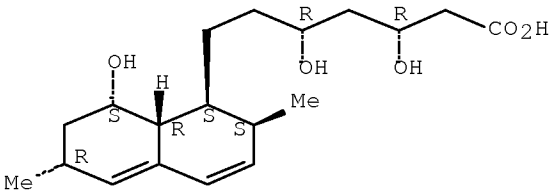
Absolute stereochemistry.



IT 132748-10-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for producing simvastatin from lovastatin)

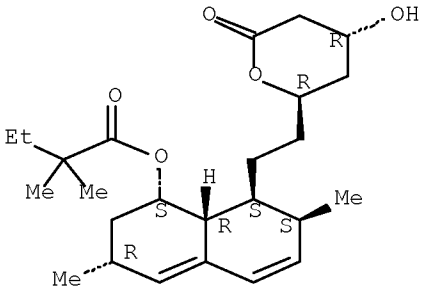
RN 132748-10-8 HCAPLUS
CN 1-Naphthaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,8-trihydroxy-2,6-dimethyl-, (βR,δR,1S,2S,6R,8S,8aR)- (CA INDEX NAME)

Absolute stereochemistry.



IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for producing simvastatin from lovastatin)
RN 79902-63-9 HCAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d iall abeq tech abex fraghitstr 18-20
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE, BIOSIS, JAPIO, BIOTECHDS' - CONTINUE? (Y)/N:y

L150 ANSWER 18 OF 29 WPIX COPYRIGHT 2009 THOMSON REUTERS on STN
ACCESSION NUMBER: 2006-758517 [78] WPIX
DOC. NO. CPI: C2006-235006 [78]
DOC. NO. NON-CPI: N2006-588907 [78]

TITLE: Process for preparation of simvastatin
DERWENT CLASS: B03
INVENTOR: BHIRUD S B; JOSHI N S; RAO K E
PATENT ASSIGNEE: (GLEN-N) GLENMARK PHARM LTD
COUNTRY COUNT: 1

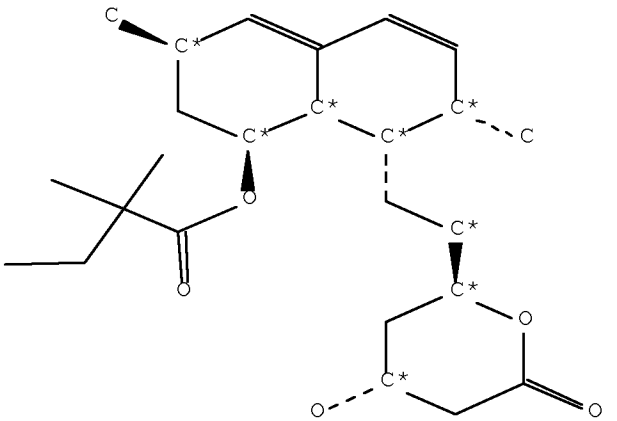
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
IN 2004MU00480	I3	20060616	(200678)*	EN	[0]	

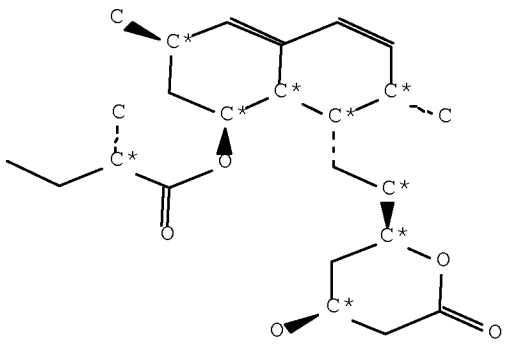
APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
IN 2004MU00480	I3	IN 2004-MU480	20040423

PRIORITY APPLN. INFO: IN 2004-MU480 20040423
INT. PATENT CLASSIF.:
MAIN: C07D309-30
BASIC ABSTRACT:
IN 200400480 I3 UPAB: 20061204
NOVELTY - Improved process for preparation of 3-hydroxy-3-methyl glutaryl-coenzyme-A (HMG-CoA) inhibitors, e.g., simvastatin, and their intermediates are described. Preparation of carboxylic acid amine salt of formula (I) is described. The process involves reacting lovastatin with an amine of formula: NH-(R 1)(R 2) (III) in an aqueous medium to obtain the carboxylic acid amine salt (I). The process further involves lithiating the carboxylic acid amine salt (I) to form the corresponding 2,2-dimethylbutyrate intermediate of formula (IIa) and lactonizing intermediate (IIa) to obtain simvastatin. An improved process for lactonization of simvastatin free acid to simvastatin using peptide-coupling reagents is also described. MANUAL CODE: CPI: B07-A02B
AN.S DCR-107036
CN.P SIMVASTATIN
CN.S 2,2-Dimethyl-butyric acid 8-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-3, 7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester
SDCN R16884



AN.S DCR-99623
CN.P LOVASTATIN
CN.S 2-Methyl-butyric acid 8-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester
SDCN R16653; R19716



L150 ANSWER 19 OF 29 WPIX COPYRIGHT 2009 THOMSON REUTERS on STN
ACCESSION NUMBER: 2005-605251 [62] WPIX
DOC. NO. CPI: C2005-182212 [62]
TITLE: Preparation of simvastatin, useful to inhibit cholesterol biosynthesis, comprises reacting lovastatin ammonium salt with a base to give a hexahydro napthalene compound, lactonising, protecting, acylating followed by deprotecting
DERWENT CLASS: B03
INVENTOR: BHADWAL P; DUBEY S K; JAIN P; KHANNA J M; THAPER R K
PATENT ASSIGNEE: (JUBI-N) JUBILANT ORGANOSYS LTD
COUNTRY COUNT: 106

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2005077928	A1	20050825	(200562)*	EN	16[0]	
IN 2004DE00201	I1	20060303	(200626)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005077928	A1	WO 2005-IN43	20050211
IN 2004DE00201	I1	IN 2004-DE201	20040210

PRIORITY APPLN. INFO: IN 2004-DE201 20040212
IN 2004-DE201 20040210
INT. PATENT CLASSIF.:
MAIN: C12N009-02
SECONDARY: C07C051-00; C12P007-62
IPC RECLASSIF.: C07D0309-00 [I,C]; C07D0309-30 [I,A]
ECLA: C07D0309-30

BASIC ABSTRACT:

WO 2005077928 A1 UPAB: 20051223

NOVELTY - Preparation of simvastatin of (I) comprises reacting lovastatin ammonium salt (II) with a base to give a hexahydro naphthalene compound (III), lactonizing (III) to give a naphthalene compound (IV), protecting the hydroxyl group of (IV) to give a naphthalene compound (V), acylating (V) to give a naphthalene compound (VI), deprotecting (VI) followed by hydrolysis with a base to give simvastatin ammonium compound (VII) and lactonizing.

DETAILED DESCRIPTION - Preparation of simvastatin of formula (I) comprises:

(A) reacting lovastatin ammonium salt of formula (II) with a base to give a hexahydro naphthalene compound of formula (III);

(B) lactonizing (III) in the presence of a lactonizing agent to give a naphthalene compound of formula (IV);

(C) selectively protecting the hydroxyl group of (IV) with a hydroxyl protecting group to give a naphthalene compound of formula (V);

(D) acylating (V) with an acylating agent using potassium halide in the presence of solvent to give a naphthalene compound of formula (VI);

(E) deprotecting (VI), in acidic condition followed by hydrolysis in the presence of a base to give simvastatin ammonium compound of formula (VII); and

(F) lactonizing.

R2 = hydroxy protecting group.

ACTIVITY - Antilipemic.

MECHANISM OF ACTION - 3-Hydroxy-3-methyl glutaryl coenzyme reductase (HMG-CoA) inhibitor.

USE - (I) is useful to inhibit cholesterol biosynthesis. No biological data given.

ADVANTAGE - (I) is prepared with minimum chemical steps, less time and use of inexpensive reagents. MANUAL CODE: CPI: B07-A02B; B14-D05D; B14-F06

TECH

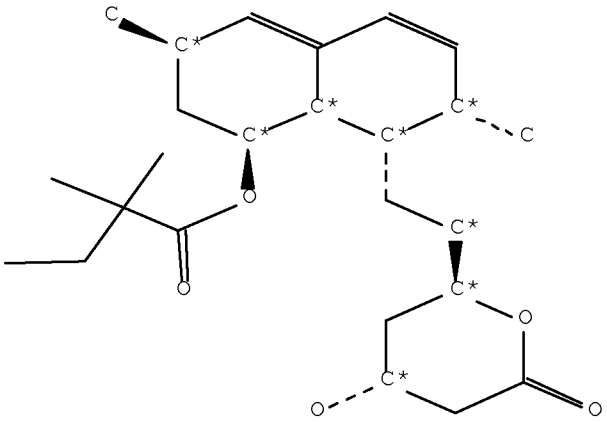
ORGANIC CHEMISTRY - Preferred Components: The base used in step (a) is hydroxides or alkoxides of alkali metal or alkaline earth metal. The alkali or alkaline earth metal is lithium, sodium, potassium or magnesium. The lactonizing agent used in step (b) is formic acid, acetic acid trifluoroacetic acid, methane sulfonic acid, p-toluene sulfonic acid or benzene sulfonic acid. The hydroxyl protecting group used in step (c) is silyl, borate, cyclic ether, cyclic thioether, an acetal, cyclic acetals or cyclic ketals. The hydroxyl protecting group is trimethylsilyl, triethylsilyl, dimethylhexylsilyl, diethylisopropylsilyl, tribenzylsilyl, tri-p-xylylsilyl, dimethylisopropylsilyl, tert-butyldimethylsilyl, tert-butylmethoxyphenylsilyl, t-butyldiphenylsilyl, diisopropylmethylsilyl, (triphenylmethyl)dimethylsilyl, diphenylmethylsilyl, triisopropylsilyl, triphenylsilyl, t-butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, phenylboronic acid, tetrahydropyran-2-yl, tetrahydrothiopyran-2-yl, 4-methoxytetrahydropyran-2-yl, 1,4-dioxane-2-yl, 1,3 dioxolanes, 4,6-dimethyl-1,3 dioxane, tetrahydrofuran-2-yl or acetonide. The acylating agent used in step (d) is 2,2-dimethylbutyrylchloride. The halide used in step (d) is fluorine, chlorine, bromine or iodine. The solvent used in step (d) is N-methyl morpholine and/or N- methyl pyrrolidine. Preferred Process: The lactonization process of step (f) is carried out by heating. (VI) is naphthalene compound of formula (VIa).

R3 = 1-5C alkyl

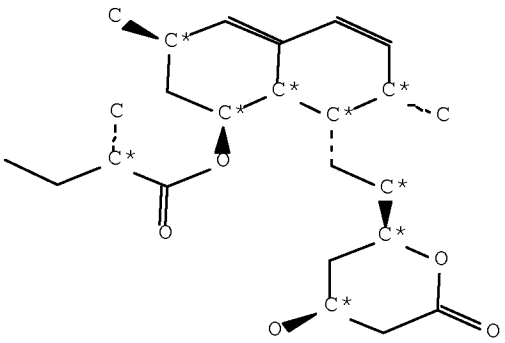
ABEX EXAMPLE - Tetrahydrofuran (400 ml) and water (10 ml) was added and cooled to 10degreesC. Lovastatin ammonium salt (100 gm) and potassium tertiary butoxide (203 gm) was added to the above solution. The reaction mixture was worked up to give

7-(1',2',6',7',8',8a'(R)-hexahydro-2'(S),6'(R)-dimethyl-8'(S)-hydroxy-1'(S)-naphthyl)-3(R),5(R)-dihydroxyheptanoic acid (III). (III) (72 g) was dissolved in dichloromethane (300 ml) and p-toluene sulfonic acid (4 g) was added to the above solution. The reaction mixture was worked up to give 6(R)-(2-(8' (S)-hydroxy-2' (S),6' (R)-dimethyl-1',2',6',7',7',8',8a'(R)-hexahydro-naphthyl-1'(S)ethyl)-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (IV). (IV) (60 g) was dissolved in dichloromethane (300 ml). Imidazole (23 gm) and t-butyldimethylchlorosilane (46 gm) were added. The reaction mixture was worked up to give 6(R)-(2-(8'(S)-hydroxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8a'(R)-hexahydro napthyl-1'(S))ethyl)-4(R)-(dimethyltertbutylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (V). Potassium iodide (9.2 g) and 2,2-dimethylbutyryl chloride (40 g) was added to a solution of (V) (50 g) in N-methyl morpholine (250 ml). The reaction mixture was worked up to give 6(R)-(2-(8' (S)-2'',2 ''-dimethylbutyryloxy-2'(S),6'(R)-dimethyl-1'.2',6',7',8',8a'(R)-hexahydronapthyl-1'(S))ethyl)-4(R)-(dimethylterbutylsilyoxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (VI). Concentrated hydrochloric acid (40 ml) was added to the solution of (VI) (90 g) in tetrahydrofuran (400 ml). The reaction mixture was worked up to give 7-(1',2',6',7',8',8a'(R)-hexahydro-2'(S),6'(R)-dimetyl-8'(S)-(2,2-dimetylbutanoyl)oxy-1'(S)-naphthyl)-3(R),5(R)-dihydroxy heptanoate (VII). Ammonium salt of (VII) (50 g) in toluene (1250 ml) was refluxed while removing water azeotropically under a constant flow of nitrogen. The reaction mixture was worked up to give 6(R)-(2-(8 '(S)-2'', 2'' -dimethylbutyrylloxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8a'(R)-hexahydronapthyl-1'(S)ethyl)-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (97%).

AN.S DCR-107036
CN.P SIMVASTATIN
CN.S 2,2-Dimethyl-butyric acid 8-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-3, 7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester
SDCN R16884



AN.S DCR-99623
CN.P LOVASTATIN
CN.S 2-Methyl-butyric acid 8-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester
SDCN R16653; R19716



L150 ANSWER 20 OF 29 WPIX COPYRIGHT 2009 THOMSON REUTERS on STN
ACCESSION NUMBER: 2003-182111 [18] WPIX
DOC. NO. CPI: C2003-047873 [18]
TITLE: Method for preparing simvastatin useful as a 3-hydroxy-3-methyl-glutaryl-coenzyme-A (HMG-CoA) reductase inhibitor for treating arteriosclerosis, comprises alkylating alpha-carbon of 2-methylbutyrate secondary chain of lovastatin
DERWENT CLASS: B03
INVENTOR: GALEAZZI E; GARCIA G A; LARA F; LOPEZ G; MARTINEZ O; TISSELLI E; TREJO A
PATENT ASSIGNEE: (FERM-N) FERMIC SA DE CV
COUNTRY COUNT: 98

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 6472542	B1	20021029	(200318)*	EN	10[0]	
WO 2003045935	A1	20030605	(200347)	EN		
AU 2002341268	A1	20030610	(200419)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6472542 B1		US 2001-996664	20011129
AU 2002341268 A1		AU 2002-341268	20020906
WO 2003045935 A1		WO 2002-IB4082	20020906

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2002341268 A1	Based on		WO 2003045935 A

PRIORITY APPLN. INFO: US 2001-996664 20011129
INT. PATENT CLASSIF.:
IPC RECLASSIF.: C07C0235-00 [I,C]; C07C0235-30 [I,A]; C07D0309-00 [I,C]; C07D0309-30 [I,A]; C07F0007-00 [I,C]; C07F0007-18 [I,A]
ECLA: C07C0235-30; C07D0309-30; C07F0007-18C4D4D;

C07F0007-18C9G
ICO: M07C0102:28
USCLASS NCLM: 549/292.000
NCLS: 560/252.000
BASIC ABSTRACT:
US 6472542 B1 UPAB: 20050528
NOVELTY - New method for preparing simvastatin comprises:
(i) reacting lovastatin and alkylamine giving lovastatin amide;
(ii) protecting hydroxyl group;
(iii) methylating 2-methylbutyrate secondary chain of protected simvastatin amide;
(iv) quenching methylating agent to obtain simvastatin amide;
(v) hydrolyzing amide to acid (A);
(vi) converting (A) to ammonium salt (S);
(vii) lactonizing (S) giving crude simvastatin followed by purification.
DETAILED DESCRIPTION - New method for preparing (P1) simvastatin of formula (VI) comprises:
(1) preparing a lovastatin amide by reacting lovastatin and an alkylamine;
(2) protecting the hydroxyl groups of the lovastatin amide by reacting the hydroxyl groups with hexamethyldisilazane (HMDS) to form a trimethylsilyl protected lovastatin amide;
(3) methylating by reacting a methylating agent with the alpha-carbon of the 2-methylbutyrate secondary chain of the trimethylsilyl protected lovastatin amide to form a trimethylsilyl protected simvastatin amide and quenching the methylating agent with water or an aqueous liquid to remove the trimethylsilyl groups and to obtain a simvastatin amide;
(4) hydrolyzing the simvastatin amide to form simvastatin acid;
(5) converting the simvastatin acid to a simvastatin ammonium salt;
(6) lactonizing the simvastatin ammonium salt to form crude simvastatin; and
(7) purifying the crude simvastatin.
INDEPENDENT CLAIMS are also included for:
(a) a method of preparing (P2) lovastatin amide of formula (IVA) comprising reacting lovastatin and an alkylamine to give a lovastatin amide followed by reacting with HMDS;
(b) a method of producing (P3) a compound of formula (VA) comprising:
(1) methylating the alpha carbon of the 2-methylbutyrate chain of (IVA) to form simvastatin amide of formula (IVB); and
(2) removing trimethylsiloxy protecting groups of (IVB) by mixing the compound with an excess of water or an aqueous liquid; and
(c) compounds of formula (IVA) and (IVB).
R = 3-5C alkyl.
ACTIVITY - Antiarteriosclerotic; Antilipemic.
MECHANISM OF ACTION - (3-Hydroxy-3-methyl-glutaryl-coenzyme-A) HMG-CoA Reductase Inhibitor.
USE - For preparing simvastatin (claimed) useful as a very active anti-hypercholesterolemic agent for treating arteriosclerosis.
ADVANTAGE - The process provides improved yields and in a purity desired for pharmaceutical use. MANUAL CODE: CPI: B05-B01B; B07-A02B; B10-D03; B14-D02A2; B14-D05D;
B14-F07; N04-B; N04-C; N04-D; N05-E02; N07-D07
TECH
ORGANIC CHEMISTRY - Preferred Method: In (P2) the mixture is heated to 45-95 (preferably 50-70) degrees C.
The methylating step involves reacting a methylating agent with an anion prepared by reacting lovastatin amide with a lithium amide formed by the reaction of a base comprising pyrrolidine and an alkyl lithium comprising n-hexyllithium.

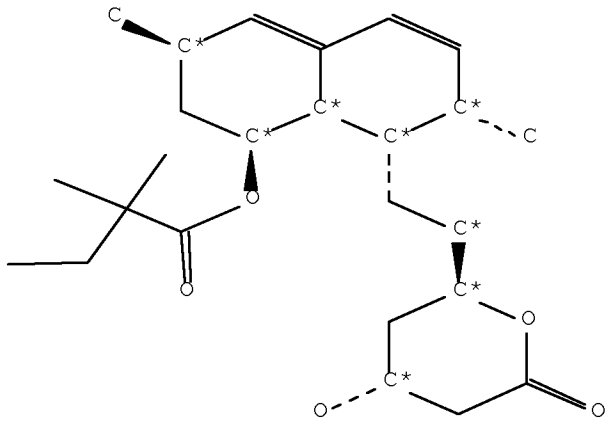
The lithium amide (preferably lithium pyrrolidine) is formed at -20 to -50 (preferably -25 to -30) degrees C.
The lactonizing step involves mixing the simvastatin ammonium salt with methylene chloride and a catalytic amount of an inorganic acid (preferably hydrochloric acid) and refluxing to remove methylene chloride.
The purifying of crude simvastatin involves adding to the crude simvastatin, ethyl alcohol (4-6 liters of per kilogram of the crude simvastatin) and precipitating simvastatin with water (4-6 liters of per kilogram of crude simvastatin).
The crude simvastatin is purified to an at least 97 wt.% purity based on the weight of the product.
The forming of the anion involves reacting lithium pyrrolidine at -20 to -50 (preferably -40 to -45) degrees C with a solution of the protected lovastatin amide for 2-4 (preferably 3-3.5) hours.
When the methylating agent is methyl iodide, the reaction temperature is -25 to -45 (preferably -28 to -32) degrees C.
The hydrolyzing of simvastatin amide involves refluxing the simvastatin amide in a mixture of methanol and 3 N solution of sodium hydroxide for 3-6 hours.
The conversion to an ammonium salt involves adding to simvastatin acid a mixture of ammonium hydroxide (1 part by volume) and methanol (3 parts by volume) followed by precipitation at 0-10 degrees C.
The lactonizing of the simvastatin ammonium salt involves mixing the ammonium salt with methylene chloride and a catalytic amount of an inorganic acid and distilling to remove methylene chloride.
The protecting step is carried out in the absence of a base.

ABEX SPECIFIC COMPOUNDS - n-Butylamine is specifically claimed as the alkylamine.

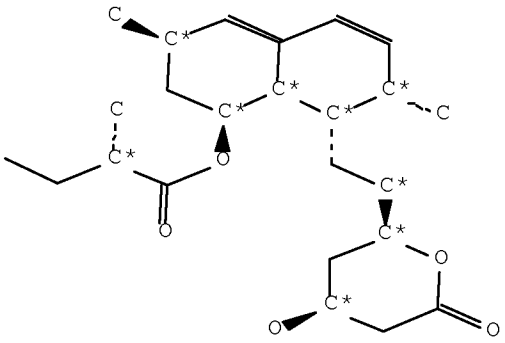
EXAMPLE - Lovastatin (20 kg) was dissolved in n-butylamine (10 l) at 45-95 degrees C. The lovastatin amide solution was concentrated at about 440 mm/Hg to remove unreacted butylamine to give lovastatin amide (a). Dimethylformamide (DMF) (40-60 l) and hexamethyldisilazane (HMDS) (20-40 l) were mixed and added to the solution of (a). The reaction was maintained under stirring at room temperature for 20-48 hours to complete the protection reaction. The mixture was dissolved in an organic phase, cyclohexane (250-400 l), and washed with water (250-400 l). The organic phase was separated for use as a methylation substrate and protected lovastatin amide (b) was obtained. A solution of pyrrolidine (14-18 l) in anhydrous tetrahydrofuran (THF) (50-70 l) was prepared under a nitrogen atmosphere, cooled to about -100 to -600 degrees C and a 1.9 M solution of hexyllithium in hexane (95-110 l) was added at -20 to -50 degrees C. Once the addition was finished, the solution was maintained at -20 to -50 degrees C for 15-45 minutes. The resultant product was lithium pyrrolidine (c) in THF. The solution of (b) in cyclohexane and anhydrous tetrahydrofuran (50-70 l) were mixed and cooled to -30 to -80 degrees C under a nitrogen atmosphere. The solution of (c) was added to the cooled lovastatin amide solution at -20 to -50 degrees C for 2-4 hours, during the addition. After anion formation, methyl iodide (5-7 l) was added to the solution of lovastatin amide anion in cyclohexane and THF. The temperature was maintained at about -25 to -45 degrees C during the addition and for 15-45 minutes afterward. The reaction was quenched with water (250-350 l). The phases were separated and the organic phase was treated with a 1 N solution of hydrochloric acid (HCl) (250-350 l). The phases were separated again and the organic phase was concentrated to a final volume of 70-100 l. The concentrated simvastatin amide solution was then cooled under a nitrogen atmosphere and was reserved for amide hydrolysis and ammonium salt precipitation. To the concentrated solution of simvastatin amide obtained was added

methanol (120-150 l) and a 3 N solution of sodium hydroxide (120-150 l). The mixture was distilled to remove methanol and then was refluxed for about 3-6 hours. The solution was concentrated to a volume of 70-100 l, cooled and a 3 N solution of HCl was added to obtain a pH of 1-2. The product was extracted and the ammonium salt was precipitated. The solution was left overnight to complete the precipitation. The product was filtered and vacuum dried to give simvastatin acid ammonium salt (d). (d) was resuspended in methylene chloride (10-20 l per kg of salt) and concentrated HCl was added (3-5 l). The mixture was distilled until the reaction was completed at about 25-45 degrees C. The organic phase was worked up to give crude simvastatin product (e). (e) was dissolved in ethanol (4-6 volume per kg) and worked up to give pure simvastatin (yield: 60-65%).

AN.S DCR-107036
CN.P SIMVASTATIN
CN.S 2,2-Dimethyl-butyric acid 8-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-3, 7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester
SDCN R16884



AN.S DCR-99623
CN.P LOVASTATIN
CN.S 2-Methyl-butyric acid 8-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester
SDCN R16653; R19716



=> d ibib ed ab ind 21-29
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE, BIOSIS, JAPIO, BIOTECHDS' - CONTINUE? (Y)/N:y

L150 ANSWER 21 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2007652624 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17697761
TITLE: Structural elucidation of an unknown Simvastatin by-product in industrial synthesis starting from Lovastatin.
AUTHOR: Bertacche Vittorio; Milanese Alberto; Nava Donatella; Pini Elena; Stradi Riccardo
CORPORATE SOURCE: Istituto di Chimica Organica A. Marchesini, Universita degli Studi, Milano, Italy.
SOURCE: Journal of pharmaceutical and biomedical analysis, (2007 Nov 30) Vol. 45, No. 4, pp. 642-7. Electronic Publication: 2007-07-10.
Journal code: 8309336. ISSN: 0731-7085.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200803
ENTRY DATE: Entered STN: 6 Nov 2007
Last Updated on STN: 4 Mar 2008
Entered Medline: 3 Mar 2008
ED Entered STN: 6 Nov 2007
Last Updated on STN: 4 Mar 2008
Entered Medline: 3 Mar 2008
AB Unknown by-product in Simvastatin synthesis from Lovastatin was found. The elucidation of this molecular structure by means of (1)H and (13)C NMR spectroscopy, HPLC/MS, MS/MS and FT-IR was shown. The mentioned by-product, originated during Merck Sharp and Dhome synthesis scheme was isolated in the second-last step replacing butylamine with benzylamine. The spectroscopic results agreed with a molecular formula C(32)H(43)NO(3). The proposed structure of this compound, characterised by the presence of a conjugated dienic system in the heptanoic acid amide residue, was alpha,beta,gamma,delta unsaturated Simvastatin N-benzylamide.
CT Chromatography, High Pressure Liquid

*Lovastatin: CH, chemistry
Magnetic Resonance Spectroscopy
Molecular Conformation
*Simvastatin: AA, analogs & derivatives
*Simvastatin: CS, chemical synthesis
Simvastatin: CH, chemistry
Spectroscopy, Fourier Transform Infrared
Tandem Mass Spectrometry
RN 75330-75-5 (Lovastatin); 79902-63-9 (Simvastatin)

L150 ANSWER 22 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2006674961 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17113998
TITLE: Biosynthesis of lovastatin analogs with a broadly specific acyltransferase.
AUTHOR: Xie Xinkai; Watanabe Kenji; Wojcicki Wladyslaw A; Wang Clay C C; Tang Yi
CORPORATE SOURCE: Department of Chemical and Biomolecular Engineering, University of California, Los Angeles, 5531 Boelter Hall, 420 Westwood Plaza, Los Angeles, California 90095, USA.
CONTRACT NUMBER: R01-GM75857 (United States NIGMS NIH HHS)
SOURCE: Chemistry & biology, (2006 Nov) Vol. 13, No. 11, pp. 1161-9.
Journal code: 9500160. ISSN: 1074-5521.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200702
ENTRY DATE: Entered STN: 21 Nov 2006
Last Updated on STN: 28 Feb 2007
Entered Medline: 27 Feb 2007
ED Entered STN: 21 Nov 2006
Last Updated on STN: 28 Feb 2007
Entered Medline: 27 Feb 2007
AB The natural product lovastatin and its semisynthetic, more effective derivative, simvastatin, are important drugs for the treatment of hypercholesterolemia. Here, we report the biochemical characterization of a dedicated acyltransferase, LovD, encoded in the lovastatin biosynthetic pathway. We demonstrate that LovD has broad substrate specificity towards the acyl carrier, the acyl substrate, and the decalin acyl acceptor. LovD can efficiently catalyze the acyl transfer from coenzyme A thioesters or N-acetylcysteamine (SNAC) thioesters to monacolin J. When alpha-dimethylbutyryl-SNAC was used as the acyl donor, LovD was able to convert monacolin J and 6-hydroxyl-6-desmethylmonacolin J into simvastatin and huvastatin, respectively. Using the Escherichia coli LovD overexpression strain as a whole-cell biocatalyst, preparative amounts of simvastatin were synthesized in a single fermentation step. Our results demonstrate LovD is an attractive enzyme for engineered biosynthesis of pharmaceutically important cholesterol-lowering drugs.
CT Acyl Coenzyme A: CH, chemistry
Acyl Coenzyme A: ME, metabolism
Acyltransferases: GE, genetics
*Acyltransferases: ME, metabolism
*Anticholesteremic Agents
Aspergillus: GE, genetics
Catalysis
Escherichia coli: ME, metabolism

Fungal Proteins: GE, genetics
*Fungal Proteins: ME, metabolism
Lovastatin: AA, analogs & derivatives
*Lovastatin: BI, biosynthesis
Mutation
Simvastatin: CS, chemical synthesis
Substrate Specificity
RN 2140-48-9 (butyryl-coenzyme A); 75330-75-5 (Lovastatin); 79902-63-9 (Simvastatin)
CN 0 (Acyl Coenzyme A); 0 (Anticholesteremic Agents); 0 (Fungal Proteins); EC 2.3.- (Acyltransferases)

L150 ANSWER 23 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2005679780 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16251252
TITLE: Acyl-coenzyme a formation of simvastatin in mouse liver preparations.
AUTHOR: Li Chunze; Subramanian Raju; Yu Sean; Prueksaritanont Thomayant
CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA.. chunze_li@merck.com
SOURCE: Drug metabolism and disposition: the biological fate of chemicals, (2006 Jan) Vol. 34, No. 1, pp. 102-10. Electronic Publication: 2005-10-26. Journal code: 9421550. ISSN: 0090-9556.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200602
ENTRY DATE: Entered STN: 22 Dec 2005
Last Updated on STN: 28 Feb 2006
Entered Medline: 27 Feb 2006
ED Entered STN: 22 Dec 2005
Last Updated on STN: 28 Feb 2006
Entered Medline: 27 Feb 2006
AB Formation of an acyl-CoA thioester has been proposed, but not directly demonstrated, to be a key step in mediating both lactonization and atypical beta-oxidation of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors. Here, we describe studies to characterize formation of acyl-CoA thioesters in vitro in mouse liver preparations using the hydroxy acid form of simvastatin (SVA) as a model substrate. With an optimized chromatography method, three new products were detected in addition to the dehydration product (P1) and the lactone form of simvastatin, which have been characterized previously (Prueksaritanont et al., 2001). Based on high-pressure liquid chromatography analysis, UV spectroscopy, mass spectrometry, and NMR spectral characterization, two metabolites were identified as acyl-CoA thioester conjugates of SVA and P1, respectively, whereas the third metabolite (M1) was confirmed to be the L-beta-hydroxy isomer of simvastatin. M1 was probably formed by stereospecific hydration, a previously reported reaction, and subsequent lactonization of P1-S-acyl CoA. Among all the mouse liver subcellular fractions, microsomes exhibited the highest capacity to catalyze the CoASH-dependent metabolism of SVA, whereas such activity was totally absent in cytosol. Together, these results provide direct experimental evidence that SVA (and conceivably other statins as well) is able to form an acyl-CoA thioester, possibly by microsomal long-chain acyl-CoA synthetase(s), leading to formation of two parallel metabolic pathways, one resulting in the two diastereomers of statin lactones (simvastatin and M1) and the other to the beta-oxidation pathway of statin hydroxy acids.
CT Acetyl-CoA C-Acyltransferase: ME, metabolism

*Acyl Coenzyme A: ME, metabolism
Adenosine Triphosphate: ME, metabolism
Animals
Chromatography, High Pressure Liquid: MT, methods
Isomerism
Magnetic Resonance Imaging: MT, methods
Mice
Microsomes, Liver: CH, chemistry
*Microsomes, Liver: ME, metabolism
Oxidation-Reduction
Simvastatin: CH, chemistry
*Simvastatin: ME, metabolism
Spectrometry, Mass, Electrospray Ionization: MT, methods
Sulfides: ME, metabolism
RN 56-65-5 (Adenosine Triphosphate); 79902-63-9 (Simvastatin)
CN 0 (Acyl Coenzyme A); 0 (Sulfides); EC 2.3.1.16 (Acetyl-CoA C-Acyltransferase)

L150 ANSWER 24 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003422521 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12963475
TITLE: Lactonase and lactonizing activities of human serum paraoxonase (PON1) and rabbit serum PON3.
AUTHOR: Teiber John F; Draganov Dragomir I; La Du Bert N
CORPORATE SOURCE: Department of Pharmacology, University of Michigan Medical School, 1150 W. Medical Center Drive, Ann Arbor, MI 48109, USA.
SOURCE: Biochemical pharmacology, (2003 Sep 15) Vol. 66, No. 6, pp. 887-96.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 10 Sep 2003
Last Updated on STN: 17 Oct 2003
Entered Medline: 16 Oct 2003
ED Entered STN: 10 Sep 2003
Last Updated on STN: 17 Oct 2003
Entered Medline: 16 Oct 2003
AB Human paraoxonase (PON1) was previously shown to hydrolyze over 30 different lactones (cyclic esters). In the present study purified human PON1 was found to catalyze the reverse reaction (lactonization) of a broad range of hydroxy acids. Hydroxy acid lactonization or lactone hydrolysis is catalyzed until equilibrium between the open and closed forms is reached. Lactonization by PON1 was calcium-dependent, had a pH optimum of 5.5-6 and could be stimulated with dilauroylphosphatidylcholine. Rabbit serum PON3 and a serine esterase in mouse plasma, presumably a carboxylesterase, also catalyzed hydroxy acid lactonization. Two endogenous oxidized unsaturated fatty acids, (+/-)4-hydroxy-5E,7Z,10Z,13Z,16Z,19Z-docosahexaenoic acid (4-HDoHE) and (+/-)5-hydroxy-6E,8Z,11Z,14Z-eicosatetraenoic acid (5-HETE) lactone, were very efficiently lactonized and hydrolyzed, respectively, by PON1. Human and mouse plasma samples also catalyzed 4-HDoHE lactonization and 5-HETE lactone hydrolysis. Studies with the PON1 inhibitor EDTA and the serine esterase inhibitor phenylmethylsulfonylfluoride suggest that about 80-95% of both activities can be attributed to PON1 in the human samples. In the mouse sample, PON1 accounted for about 30% of the 4-HDoHE lactonizing activity and 72% of the 5-HETE lactonase activity. Our results demonstrate that PON1 can

lactonize the hydroxy acid form of its lactone substrates and that reversible hydrolysis of lactones may be a property of lactonases that is not generally considered. Also, the high activity of PON1 towards 4-HDoHE and 5-HETE lactone suggests that oxidized eicosanoids and docosanoids may be important physiological substrates for PON1.

CT Animals
Aryldialkylphosphatase
*Esterases: ME, metabolism
Fatty Acids: ME, metabolism
Humans
*Lactones: ME, metabolism
Lovastatin: ME, metabolism
Mice
Rabbits
Simvastatin: ME, metabolism
Species Specificity
Substrate Specificity

RN 75330-75-5 (Lovastatin); 79902-63-9 (Simvastatin)

CN 0 (Fatty Acids); 0 (Lactones); EC 3.1.- (Esterases); EC 3.1.- (PON3 protein, human); EC 3.1.8.1 (Aryldialkylphosphatase); EC 3.1.8.1 (PON1 protein, human)

L150 ANSWER 25 OF 29 EMBASE

ACCESSION NUMBER: 2001337305 EMBASE Full-text
TITLE: β-oxidation of simvastatin in mouse liver preparations.
AUTHOR: Prueksaritanont, T., Dr. (correspondence); Ma, B.; Fang, X.; Subramanian, R.; Yu, J.; Lin, J.H.
CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, United States. thomayant_prueksaritanont@merck.com
SOURCE: Drug Metabolism and Disposition, (2001) Vol. 29, No. 10, pp. 1251-1255.
Refs: 19
ISSN: 0090-9556 CODEN: DMDSAI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Oct 2001
Last Updated on STN: 11 Oct 2001
ED Entered STN: 11 Oct 2001
Last Updated on STN: 11 Oct 2001

AB All current 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors [simvastatin (SV), lovastatin (LV), atorvastatin, pravastatin, fluvastatin, and cerivastatin] are believed to undergo an atypical β-oxidation of the dihydroxy heptanoic or heptanoic acid side chain. Metabolites, which are shortened by two- and/or four-carbon units consistent with β-oxidation products, have been reported exclusively in rodents following LV and SV administration and across species (rodents, dogs, and humans) following the other statins. In this study, in vitro formation of a β-oxidation product of simvastatin hydroxy acid (SVA) and its intermediates in mouse livers is described. Incubation of SVA with mouse liver preparations fortified with CoASH and ATP led to formation of SV and two major products (P1 and P2). Based on mass spectrometry (MS), tandem mass spectrometry, and/or NMR spectral characteristics, P1 was an α,β-unsaturated metabolite, formed by dehydration of the D,D-dihydroxy heptanoic

acid side chain, whereas P2 was probably the L,D-dihydroxy acid isomer of SVA, formed by stereospecific hydration of P1. When NAD(+) was also included in the incubation mixture, there were two additional metabolites with the MS and/or NMR characteristics consistent with a two-carbon shortened product (P3) and its dehydrated derivative (P4). In a complete incubation system with all cofactors (ATP, CoASH, NAD(+), and NADPH) present, there was an additional product with MS spectra and liquid chromatography retention time identical to the β-oxidized, unsubstituted pentanoic acid metabolite (P5) detected in rats and mice following simvastatin administration. The involvement of CoASH and NAD(+) and the presence of the four metabolic intermediates suggest that SVA (and presumably the other statins) is a substrate for the β-oxidation enzyme complex in mice. Additionally, the present finding of CoASH-dependent formation of SV substantiates a mechanism proposed previously for the in vivo lactonization of statin hydroxy acids.

CT Medical Descriptors:
animal tissue
article
controlled study
*drug oxidation
fatty acid oxidation
liquid chromatography
male
mouse
nonhuman
nuclear magnetic resonance spectroscopy
priority journal
stereospecificity
tandem mass spectrometry

CT Drug Descriptors:
adenosine triphosphate
atorvastatin
cerivastatin
fluindostatin
hydroxymethylglutaryl coenzyme A reductase inhibitor
mevinolin
nicotinamide adenine dinucleotide
pravastatin
reduced nicotinamide adenine dinucleotide phosphate
*simvastatin

RN (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5; (atorvastatin) 134523-00-5, 134523-03-8; (cerivastatin) 143201-11-0; (fluindostatin) 93957-54-1; (mevinolin) 75330-75-5; (nicotinamide adenine dinucleotide) 53-84-9; (pravastatin) 81131-74-0; (reduced nicotinamide adenine dinucleotide phosphate) 53-57-6; (simvastatin) 79902-63-9

L150 ANSWER 26 OF 29 EMBASE

ACCESSION NUMBER: 2000272011 EMBASE Full-text
TITLE: Direct-injection LC-MS-MS method for high-throughput simultaneous quantitation of simvastatin and simvastatin acid in human plasma.
AUTHOR: Jemal, Mohammed (correspondence); Ouyang, Zheng; Powell, Mark L.
CORPORATE SOURCE: Bioanalytical Research, Metab. Pharmacokin., Bristol-M., New Brunswick, NJ 08903-0191, United States. jemalm@bms.com
AUTHOR: Jemal, Mohammed (correspondence)
CORPORATE SOURCE: Bioanalytical Research, Bristol-Myers Squibb, Pharmaceutical Research Institute, P.O. Box 191, New Brunswick, NJ 08903-0191, United States. jemalm@bms.com

SOURCE: Journal of Pharmaceutical and Biomedical Analysis, (15 Aug 2000) Vol. 23, No. 2-3, pp. 323-340.
Refs: 15
ISSN: 0731-7085 CODEN: JPBADA
PUBLISHER IDENT.: S 0731-7085(00)00309-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 17 Aug 2000
Last Updated on STN: 17 Aug 2000
ED Entered STN: 17 Aug 2000
Last Updated on STN: 17 Aug 2000

AB A direct-injection liquid chromatography-mass spectrometry-mass spectrometry (LC-MS-MS) method was developed and validated for the simultaneous quantitation in human plasma of the widely used cholesterol-lowering prodrug simvastatin and its in vivo generated active drug, simvastatin acid. The plasma samples were injected into the LC-MS-MS system after simply adding the internal standard solution in an aqueous buffer and centrifuging. The analytes in the buffered plasma samples were found to be stable for at least 24 h at 4°C. The method was successfully validated under the challenging condition of using a large number of quality control (QC) samples including those in which the ratio of the simvastatin concentration to the simvastatin acid concentration was different from the concentration ratio in the calibration curve standards. Under the dual stabilizing conditions of lower temperature (4°C) and lower plasma pH of 4.9, the in-process hydrolysis of simvastatin to simvastatin acid or the lactonization of simvastatin acid to simvastatin was minimized to ≤1.0%. Although the entire run time for on-line cleanup and analysis was only 2.5 min, chromatographic base-line separation of simvastatin from simvastatin acid, which was required to avoid the interference by simvastatin acid with the simvastatin selected reaction monitoring channel, was achieved. The desired lower limit of quantitation of 0.5 ng/ml was achieved by injecting only an equivalent of 8.0 μl of the plasma sample. The extraction column lasted for at least 500 injections. Copyright (C) 2000 Elsevier Science B.V.

CT Medical Descriptors:
accuracy
article
blood pH
calibration
controlled study
*drug blood level
*drug determination
human
human tissue
*liquid chromatography
mass spectrometry
priority journal
quality control
technique
CT Drug Descriptors:
*drug metabolite: AN, drug analysis
*drug metabolite: CR, drug concentration
mevinolin: AN, drug analysis
*simvastatin: AN, drug analysis
*simvastatin: CR, drug concentration
simvastatin acid: AN, drug analysis
simvastatin acid: CR, drug concentration

unclassified drug
RN (mevinolin) 75330-75-5; (simvastatin) 79902-63-9
CO Bristol Myers Squibb

L150 ANSWER 27 OF 29 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:20350 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400022207
TITLE: Process of lactonization in the preparation of statins.
AUTHOR(S): Lee, Kwang-Hyeg [Inventor, Reprint Author]; Kim, Jin-Wan [Inventor]; Yoon, Myeong-Sik [Inventor]; Choi, Kwang-Do [Inventor]; Lee, Sang-Ho [Inventor]; Cho, Hong-Suk [Inventor]
CORPORATE SOURCE: Seongnam Si, South Korea
ASSIGNEE: Cheil Jedang Corporation, Seoul, South Korea
PATENT INFORMATION: US 6649775 20031118
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov 18 2003) Vol. 1276, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003
ED Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003
AB The present invention relates to a process for preparing lovastatin and simvastatin which comprises (1) performing step of a lactonization of mevinic acid and analog thereof compounds in the presence of a dehydrating agent and without an acid catalyst under nitrogen sweep; and then (2) making step of crystals at a high temperature. In the process of the present invention, lovastatin and simvastatin highly purified can be produced in a high yield and especially, heterodimers formed as a by-product can be reduced in an amount remarkably. Therefore, the process of the present invention is convenient and economical.
NCL 549292000
CC Biochemistry studies - General 10060
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Cardiovascular system 22010
IT Major Concepts
Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
lovastatin: HMG CoA reductase inhibitor-drug, cardiovascular-drug, enzyme inhibitor-drug; simvastatin: HMG CoA reductase inhibitor-drug, cardiovascular-drug, enzyme inhibitor-drug
IT Methods & Equipment
lactonization process: laboratory techniques; statin preparation: laboratory techniques
RN 75330-75-5 (lovastatin)
79902-63-9 (simvastatin)

L150 ANSWER 28 OF 29 JAPIO (C) 2009 JPO on STN
ACCESSION NUMBER: 2003-183271 JAPIO Full-text
TITLE: NEW METHOD OF LACTONIZATION IN PREPARATION OF STATINS
INVENTOR: LEE KWANG-HYEG; KIM JIN-WAN; CHOI KWANG-DO; LEE

SANG-HO; CHO HONG-SUK
PATENT ASSIGNEE(S): CJ CORP
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2003183271	A	20030703	Heisei	C07D309-30

APPLICATION INFORMATION
STN FORMAT: JP 2002-350255 20021202
ORIGINAL: JP2002350255 Heisei
PRIORITY APPLN. INFO.: KR 2001-200175991 20011203
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2003
ED 20031113
AB PROBLEM TO BE SOLVED: To provide a method for preparing a lactone compound by which the lactone compound can simply and economically be prepared, while remark ably reducing the content of a dimer. SOLUTION: This method for preparing lovastatin and simvastatin comprises the steps of performing the lactonization of mevinic acid and its homologous compound in the presence of a mixed organic solvent without an acid catalyst through nitrogen sweep, and making crystals. The lovastatin and simvastatin highly purified can be produced in a high yield and especially, heterodimers formed as by-products can be reduced remarkably. Therefore, the method is convenient and economical. COPYRIGHT: (C)2003,JPO
IC ICM C07D309-30
ICS A61P003-06; A61P043-00
ICA A61K031-366

L150 ANSWER 29 OF 29 BIOTECHDS COPYRIGHT 2009 THOMSON REUTERS on STN
ACCESSION NUMBER: 1993-10980 BIOTECHDS Full-text
TITLE: Triol acid and HMG-CoA-reductase-inhibitor; simvastatin production and purification by lovastatin hydrolysis usin g Clonostachys compactiuscula hydrolase; application as an anticholes terolemic
PATENT ASSIGNEE: Merck-USA
PATENT INFO: US 5223415 29 Jun 1993
APPLICATION INFO: US 1992-832545 7 Feb 1992
PRIORITY INFO: US 1992-832545 7 Feb 1992
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 1993-219583 [27]
AB Triol acids (A) are produced by enzymatic hydrolysis of lovastatin ac id or a salt by treating it with Clonostachys compactiuscula ATCC 380 29 or ATCC 74178, or a mutant, or a hydrolase derived from these. Al so claimed is the direct production of simvastatin (B) by direct meth ylation of lovastatin or by selective hydrolysis of residual lovastat in salt by treatment with C. compactiuscula ATCC 38029 or ATCC 74178, or a mutant, or a hydrolase derived from these which can be easily s eparated from simvastatin. The hydrolase is preferably in purified f orm and is immobilized on a column. This process additionally compri ses conversion to the corresponding lactone. Separation and purifica tion is by HPLC or crystallization and the diol lactone (A) or simvas tatin is recovered. Lactonization is achieved with isopropylacetate and methane sulfonic acid. (A) and (B) are HMG-CoA-reductase-inhibit ors and may be used as anticholesterolemic agents. In an example, 0. 5 g/l lovastatin ammonium salt was added to a C. compactiuscula to in duce hydrolytic activity and after 16 hr, 60% of the starting materia l was converted to a triol acid. (16pp)
AN 1993-10980 BIOTECHDS Full-text

CC D PHARMACEUTICALS; D5 Other Pharmaceuticals; K BIOCATALYSIS; K2 Application

CT TRIOL ACID PREP., SIMVASTATIN PREP., PURIFICATION, LOVASTATIN HYDROLY SIS, CLONOSTACHYS COMPACTIUSCULA HYDROLASE, APPL. HMG-COA-REDUCTASE-I NHIBITOR, ANTICHOLESTEROLEMIC ENZYME-INHIBITOR FUNGUS ANTIARTERIOSCLEROTIC CYCLOALKANE HET-O RING-6 COND.RING LACTONE OLEFIN C-ESTER FATTY-ACID ALCOHOL ENZYME IMMOBILIZ ATION

```
=> d que nos l81
L6              STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L13             STR
L15         199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16             STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L20             STR
L22          18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24             STR
L26           5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28             STR
L30         800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L73         823 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 OR L26 OR L30
L74          59 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L18/PRO
L75          67 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L15/NPRO
L76          34 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L74 AND L75
L77           8 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L22
L78           6 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L76 AND L77
L79           9 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L73
L80           6 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L78 AND L79
L81           1 SEA FILE=CASREACT SPE=ON  ABB=ON  PLU=ON  L80 AND (L31 OR L32
                OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)


=> d que nos l71
L3  (         1)SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  US2007-576122/APPS
L4              SEL  PLU=ON  L3 1- RN :      30 TERMS
L5           30 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L4
L6              STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L8            9 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L5 AND MAN/CI
L9            3 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L8 NOT SEQUENCE/FS
L13             STR
L15         199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16             STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L20             STR
L22          18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24             STR
L26           5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28             STR
L30         800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
```

```
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L48             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLYSIS+PFT,OLD,NEW,NT/CT
L49             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIZATION+PFT,OLD,NEW,NT
                /CT
L50             QUE  SPE=ON  ABB=ON  PLU=ON  ACETYLATION+PFT,OLD,NEW,NT/C
                T
L51             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLATION+PFT,OLD,NEW,NT/CT
L52             QUE  SPE=ON  ABB=ON  PLU=ON  DEACETYLATION+PFT,OLD,NEW,NT
                /CT
L53             QUE  SPE=ON  ABB=ON  PLU=ON  DEACYLATION+PFT,OLD,NEW,NT/C
                T
L55          5405 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L18
L56           159 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L55 (L)(PREP+NT)/RL
L57          4264 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L15
L58           162 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L57 (L)(RACT+NT)/RL
L59            69 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L56 AND L58
L60            26 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L22
L61             3 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L26
L62            40 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L30
L63             9 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L59 AND (L60 OR L61
                OR L62)
L64            13 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L59 AND L49
L66             1 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L59 AND L9
L67             1 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L59 AND (L48(L)L44)
L68            19 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L63 OR L64 OR (L66 OR
                L67)
L69            19 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L68 AND (L41 OR L42
                OR L43 OR L44 OR L45 OR L46 OR L47 OR L48 OR L49 OR L50 OR L51
                OR L52 OR L53)
L70            19 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L68 OR L69
L71             2 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L70 AND (L31 OR L32
                OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)


=> d que l99
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
```

```
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L54             QUE  SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHET
                IC? OR PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD?
                OR MAKE OR MAKING OR MADE OR PROCESS? OR GIVE OR GIVING O
                R GAVE OR FORMING OR FORM OR FORMATION OR FORMS OR FORMED
L84           1 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  LOVASTATIN/CN
L85          97 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  99623/DCSE
L86        1315 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  R16653/DCN OR R19716/DCN
                OR L85/DCR OR L84/DCR
L87          36 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L86(T)(S OR RCT)/DCN,DCR

L88           1 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN/CN
L89           5 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  107036/DCSE
L90        1291 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L88/DCR OR L89/DCR OR
                R16884/DCN
L91          87 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L90 (T) (P OR PRD)/DCN,DC
                R
L92          21 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L87 AND L91
L93           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L92 AND L46
L94           4 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L93 AND (L47 OR DEACYL?/B
                IX,BIEX,ABEX,TT OR ACETYLAT?/BIX,BIEX,ABEX,TT OR DEACETYLAT?/BI
                X,BIEX,ABEX,TT)
L95           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  (L93 OR L94)
L96           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L95 AND (L41 OR L42 OR
                L43 OR L44 OR L45 OR L46 OR L47)
L97           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L95 AND L54
L98           8 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  (L95 OR L96 OR L97)
L99           1 SEA FILE=WPIX SPE=ON  ABB=ON  PLU=ON  L98 AND (L31 OR L32 OR
                L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)


=> d que nos l115
L6              STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L13             STR
L15         199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16             STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
```

```
L103       3947 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L18
L104            QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN+PFT,OLD,NEW,NT/C
                T (P)CS/CT
L105       3692 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L15
L106       3947 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L103 OR L104
L107            QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN+PFT,OLD,NEW,NT/CT
                 (P) CH/CT
L108       3733 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L105 OR L107
L109       1133 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L106 AND L108
L110          2 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L109 AND L104
L111          2 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L109 AND L46
L112          4 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  (L110 OR L111)
L113          4 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L112 AND (L41 OR L42
                OR L43 OR L44 OR L45 OR L46 OR L47)
L114          4 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L112 OR L113
L115          0 SEA FILE=MEDLINE SPE=ON  ABB=ON  PLU=ON  L114 AND (L31 OR L32
                OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)


=> d que nos l131
L6              STR
L7         5368 SEA FILE=REGISTRY SSS FUL L6
L13             STR
L15         199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16             STR
L18         202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L20             STR
L22          18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24             STR
L26           5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28             STR
L30         800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L54             QUE  SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHET
                IC? OR PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD?
                OR MAKE OR MAKING OR MADE OR PROCESS? OR GIVE OR GIVING O
                R GAVE OR FORMING OR FORM OR FORMATION OR FORMS OR FORMED
L73          823 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 OR L26 OR L30
L117       15476 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L18
L118         381 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L54(5A)(L42 OR L43)
L119        9261 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L15
L122        4661 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L117 AND L119
L123           0 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L73
```

```
L124          65 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L122 AND (L123 OR
                 L118)
L125          15 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L124 AND (L46 OR
                 LACTONE)
L126           0 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L125 AND (L47 OR
                 ACETYLAT? OR DEACYL? OR DEACETYL?)
L127          15 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  (L125 OR L126)
L128          15 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L127 AND (L41 OR L42
                 OR L43 OR L44 OR L45 OR L46 OR L47)
L129          15 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  (L127 OR L128)
L130           2 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L129 AND L46
L131           0 SEA FILE=EMBASE SPE=ON  ABB=ON  PLU=ON  L130 AND (L31 OR L32
                 OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)


=> d his l142

     (FILE 'BIOSIS, CABA, BIOTECHNO, DRUGU, VETU' ENTERED AT 10:53:32 ON 23
     JUN 2009)
L142           0 S L141 AND L31-L40

=> d que nos l142
L6                STR
L7          5368 SEA FILE=REGISTRY SSS FUL L6
L13               STR
L15          199 SEA FILE=REGISTRY SUB=L7 SSS FUL L13
L16               STR
L18          202 SEA FILE=REGISTRY SUB=L7 SSS FUL L16
L20               STR
L22           18 SEA FILE=REGISTRY SUB=L7 SSS FUL L20
L24               STR
L26            5 SEA FILE=REGISTRY SUB=L7 SSS FUL L24
L28               STR
L30          800 SEA FILE=REGISTRY SUB=L7 SSS FUL L28
L31               QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32               QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33               QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34               QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35               QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36               QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37               QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38               QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39               QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40               QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                  PA
L41               QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42               QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43               QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44               QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45               QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46               QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47               QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L54               QUE  SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHET
                  IC? OR PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD?
                  OR MAKE OR MAKING OR MADE OR PROCESS? OR GIVE OR GIVING O
                  R GAVE OR FORMING OR FORM OR FORMATION OR FORMS OR FORMED
L73           823 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 OR L26 OR L30
L133        10730 SEA L18
L134         5907 SEA L15
L135         1252 SEA L133 AND L134
```

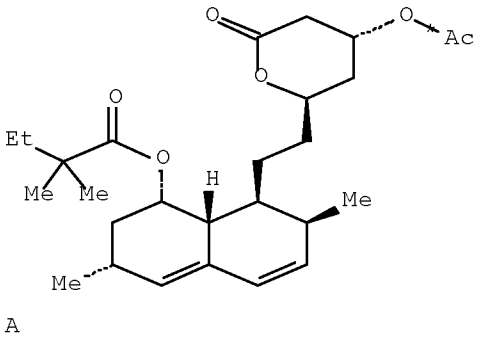
```
L136          0 SEA L73
L137        100 SEA (L54 (5A) L42) (8A) L41
L138         45 SEA L135 AND ((L136 OR L137))
L139          1 SEA L138 AND L46
L140          1 SEA L139 AND (L41 OR L42 OR L43 OR L44 OR L45 OR L46 OR L47)
L141          1 SEA L139 OR L140
L142          0 SEA L141 AND (L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR
                L38 OR L39 OR L40)


=> d his l148

     (FILE 'PASCAL, JAPIO, LIFESCI, BIOENG, BIOTECHDS, DRUGB, VETB, SCISEARCH,
     CONFSCI, DISSABS, RDISCLOSURE' ENTERED AT 10:57:03 ON 23 JUN 2009)
L148          1 S L147 AND L31-L40

=> d que l148
L31             QUE  SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32             QUE  SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33             QUE  SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34             QUE  SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35             QUE  SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36             QUE  SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37             QUE  SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39             QUE  SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40             QUE  SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,
                PA
L41             QUE  SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42             QUE  SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43             QUE  SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44             QUE  SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45             QUE  SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46             QUE  SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47             QUE  SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L54             QUE  SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHET
                IC? OR PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD?
                OR MAKE OR MAKING OR MADE OR PROCESS? OR GIVE OR GIVING O
                R GAVE OR FORMING OR FORM OR FORMATION OR FORMS OR FORMED
L144           77 SEA (L54 (5A) L42) (8A) L41
L145            3 SEA L144 AND L46
L146            3 SEA L145 AND (L41 OR L42 OR L43 OR L44 OR L45 OR L46 OR L47)
L147            3 SEA (L145 OR L146)
L148            1 SEA L147 AND (L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR
                  L38 OR L39 OR L40)


=> dup rem l81 l71 l99 l115 l131 l142 l148
L115 HAS NO ANSWERS
L131 HAS NO ANSWERS
L142 HAS NO ANSWERS
DUPLICATE IS NOT AVAILABLE IN 'RDISCLOSURE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'CASREACT' ENTERED AT 11:10:12 ON 23 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'HCAPLUS' ENTERED AT 11:10:12 ON 23 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
```

```
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIX' ENTERED AT 11:10:12 ON 23 JUN 2009
COPYRIGHT (C) 2009 THOMSON REUTERS

FILE 'BIOTECHDS' ENTERED AT 11:10:12 ON 23 JUN 2009
COPYRIGHT (C) 2009 THOMSON REUTERS
PROCESSING COMPLETED FOR L81
PROCESSING COMPLETED FOR L71
PROCESSING COMPLETED FOR L99
PROCESSING COMPLETED FOR L115
PROCESSING COMPLETED FOR L131
PROCESSING COMPLETED FOR L142
PROCESSING COMPLETED FOR L148
L151          2 DUP REM L81 L71 L99 L115 L131 L142 L148 (3 DUPLICATES REMOVED)
                ANSWER '1' FROM FILE CASREACT
                ANSWER '2' FROM FILE HCAPLUS

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 11:10:25 ON 23 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jun 19, 2009 (20090619/UP).
```

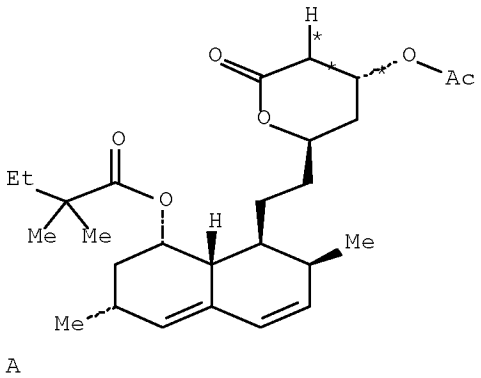
```
=> d ibib abs hit
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, CASREACT' - CONTINUE? (Y)/N:y



L151 ANSWER 1 OF 2  CASREACT  COPYRIGHT 2009 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         142:463506  CASREACT  Full-text
TITLE:                    Methods for making simvastatin and intermediates from
                          lovastatin
INVENTOR(S):              Morgan, Brian; Burk, Mark;
                          Levin, Michael; Zhu, Zoulin;
                          Chaplin, Jennifer; Kustedjo, Karen;
                          Huang, Zilin; Greenberg, William
PATENT ASSIGNEE(S):       Diversa Corporation, USA
SOURCE:                   PCT Int. Appl., 148 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2005040107      A2   20050506       WO 2004-US34913  20041020
     WO 2005040107      A3   20090212
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG, AP, EA, EP, OA
     AU 2004284068      A1   20050506       AU 2004-284068   20041020
     CA 2543348         A1   20050506       CA 2004-2543348  20041020
     EP 1678131         A2   20060712       EP 2004-817331   20041020
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR
     JP 2007519396      T    20070719       JP 2006-536794   20041020
     MX 2006004448      A    20060710       MX 2006-4448     20060421
     IN 2006KN01085     A    20090410       IN 2006-KN1085   20060426
     KR 2006129196      A    20061215       KR 2006-709870   20060519
     CN 101415833       A    20090422       CN 2004-80036202 20060605
     US 20080182303     A1   20080731       US 2007-576122   20070827
PRIORITY APPLN. INFO.:                      US 2003-513237P  20031021
                                            US 2004-542100P  20040204
                                            WO 2004-US34913  20041020
OTHER SOURCE(S):          MARPAT 142:463506
GI



* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *
```

AB The invention provides synthetic chemical and chemoenzymic methods of producing simvastatin (I) and various intermediates, e.g., triol II, acylates III [R = H, Me, (un)branched, (un)substituted C1-20-alkyl, (un)substituted Ph (especially Ph, C6H4NO2-4), OR'; R' = any of previous R] and dimethylbutyrates IV. The method comprises: (a) enzymic hydrolysis of lovastatin, lovastatin acid or salt to triol acid (II) or triol acid salt; (b) lactonization and acylation of the triol acid to form 4-acetyl lactone III (R = Me), wherein the acylation protects a 4-position hydroxyl (4'-OH) on the lactone ring by regioselective acylation of the 4'-OH; (c) enzymic acylation of an 8-position hydroxyl (8'-OH) of the 4-acetyl lactone III (R = Me) to form 4-acetylsimvastatin (IV; R = Me); and (d) selectively removing the acyl group at the 4'-position either chemical or enzymically, thereby yielding I. In one aspect, enzymes such as hydrolases, e.g., esterases, are used in the methods of the invention.

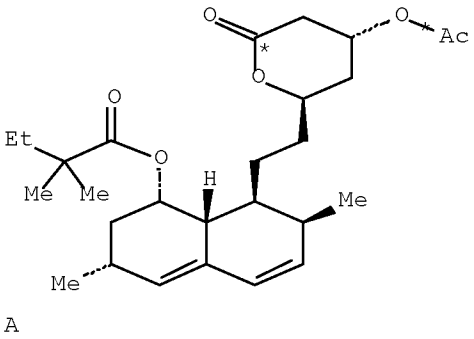
RX(1) OF 42 ...3 A ===> B + C + D...



A

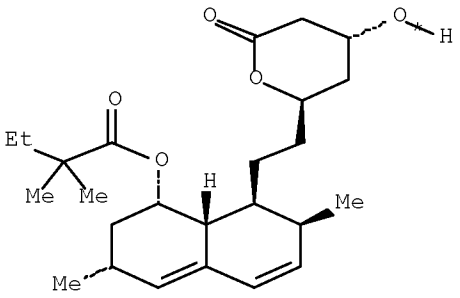


A

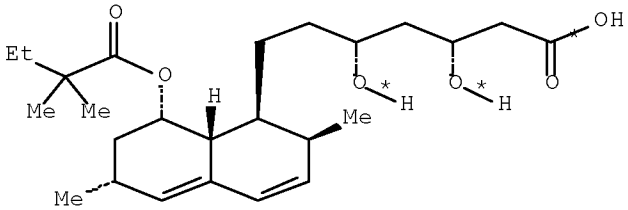


A

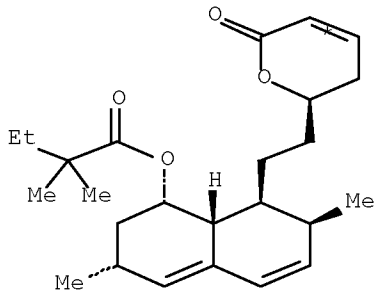
(1)



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

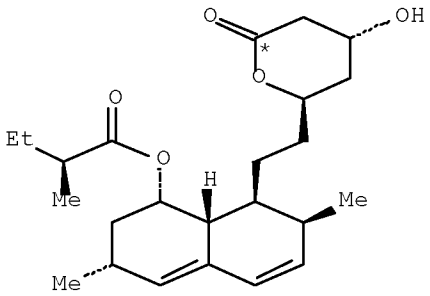
STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ

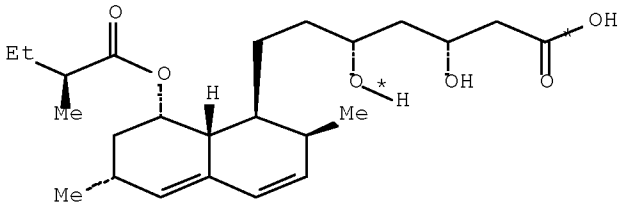
ID NO:3)]; first three stages buffer; third stage DasGip
STIRRER-PRO pH-stat system

RX(2) OF 42 K ===> L...



K

(2)



L

RX(2)

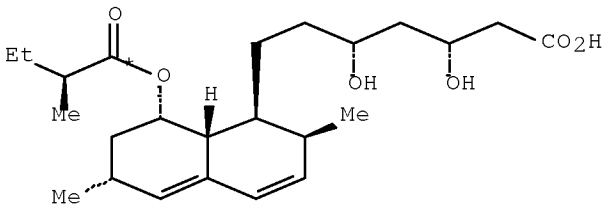
STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 35 deg C

STAGE(2)
RCT K 75330-75-5
CON 35 deg C

STAGE(3)
SOL 7732-18-5 Water
CON 35 deg C, 8 atm

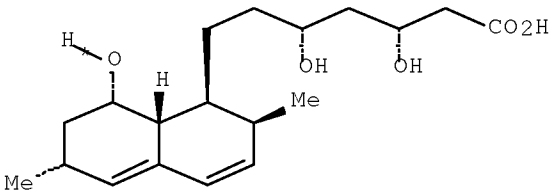
PRO L 75225-51-3
NTE reactant added in portions alternating with water over 2 h

RX(3) OF 42 ...L ===> N...



L

(3)



N
YIELD 95%

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

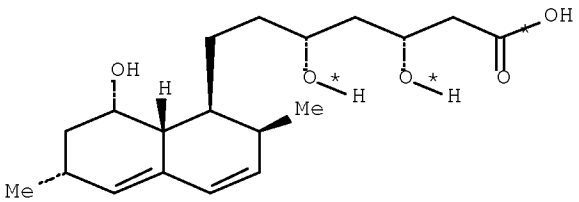
STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

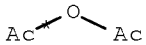
STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) OF 42 ...N + P ===> Q...

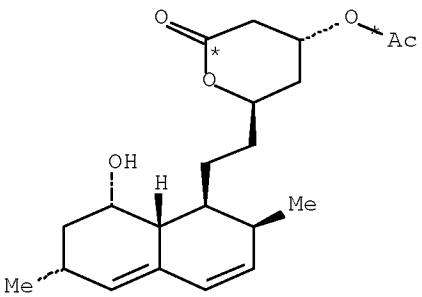


N



P

(4) →



Q
YIELD 81%

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

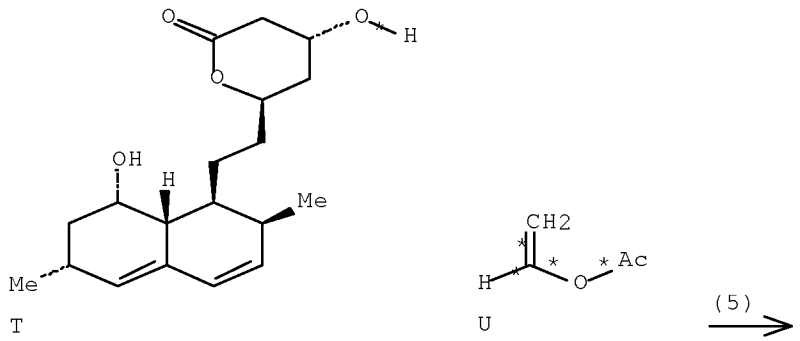
STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

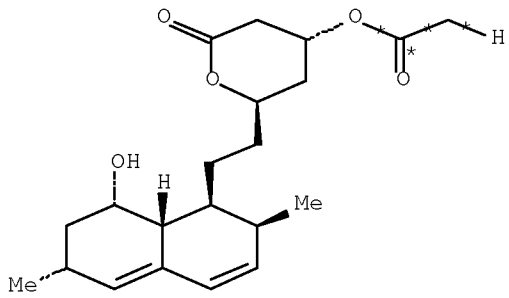
STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(5) OF 42 ...T + U ===> Q...



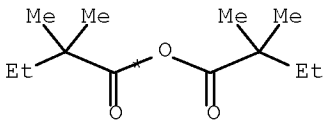
T U



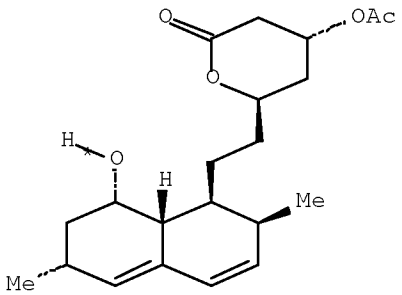
Q
YIELD 60%

RX(5) RCT T 79952-42-4, U 108-05-4
PRO Q 145576-24-5
CAT 9001-62-1 Lipase
SOL 1634-04-4 t-BuOMe
CON 44 hours, room temperature
NTE biotransformation, enzymic [lipase B (Candida antarctica)]

RX(6) OF 42 ...X + Q ===> A...

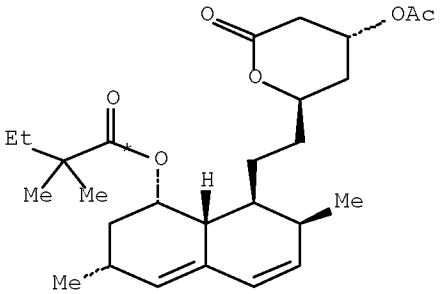


X



Q

(6)



A
YIELD 99%

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

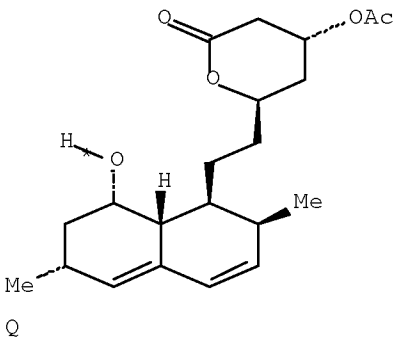
STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

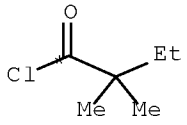
STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(8) OF 42 ..Q + AC ===> A..

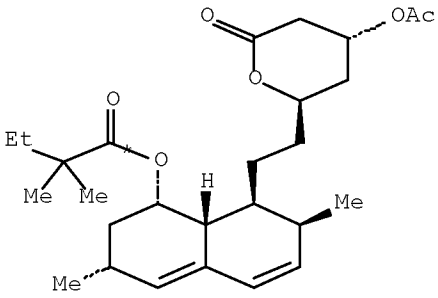


Q



AC

(8)



A
YIELD 97%

RX(8) RCT Q 145576-24-5

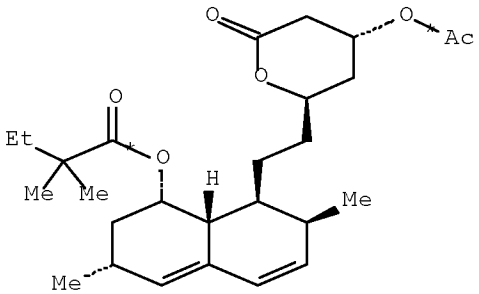
STAGE(1)
SOL 110-86-1 Pyridine

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 110-86-1 Pyridine

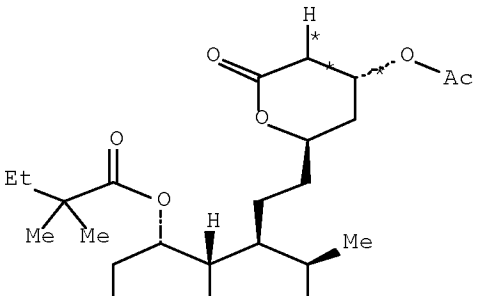
STAGE(3)
RCT AC 5856-77-9
SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

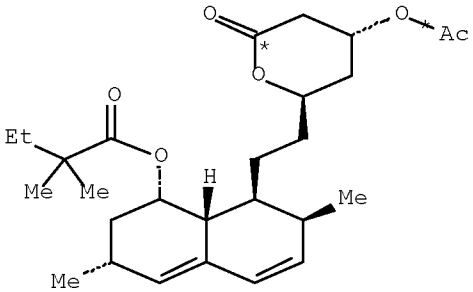
RX(9) OF 42 COMPOSED OF RX(1), RX(7)
RX(9) 3 A ===> T



A

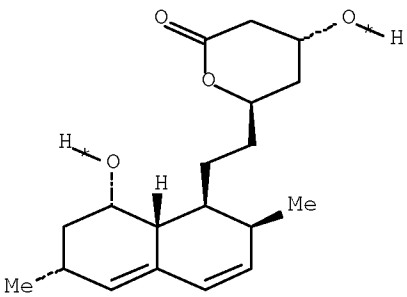


A



A

2
STEPS

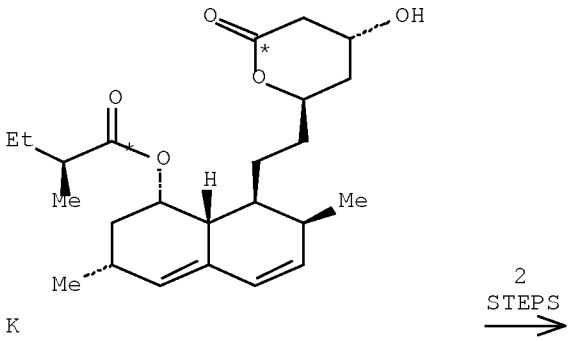


T
YIELD 80%

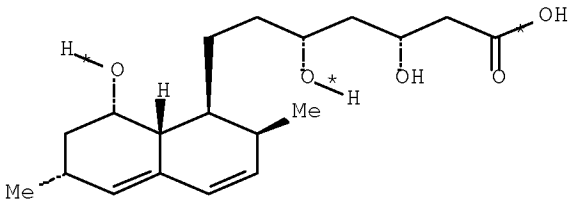
RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH

```
                CON  room temperature

              STAGE(2)
                CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
                SOL  7732-18-5 Water
                CON  room temperature

              STAGE(3)
                RGT  F 1336-21-6 NH4OH
                SOL  7732-18-5 Water
                CON  room temperature

              STAGE(4)
                SOL  108-88-3 PhMe
                CON  overnight, room temperature

            PRO  B 79902-63-9, C 121009-77-6, D 210980-68-0
            NTE  biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ
                 ID NO:3)]; first three stages buffer; third stage DasGip
                 STIRRER-PRO pH-stat system

RX(7)       RCT  B 79902-63-9

              STAGE(1)
                CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
                SOL  7732-18-5 Water, 67-56-1 MeOH

              STAGE(2)
                RGT  F 1336-21-6 NH4OH
                SOL  7732-18-5 Water
                CON  48 hours, pH 9 - 9.5

              STAGE(3)
                RGT  AA 13968-08-6 Hydronium (H3O+)
                SOL  7732-18-5 Water
                CON  pH 2

              STAGE(4)
                SOL  108-21-4 Acetic acid, 1-methylethyl ester
                CON  reflux

            PRO  T 79952-42-4
            NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
                 SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark
                 trap


RX(10) OF 42 COMPOSED OF RX(2), RX(3)
RX(10)    K  ===>  N
```



K



N
YIELD 95%

RX(2)

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 35 deg C

STAGE(2)
RCT K 75330-75-5
CON 35 deg C

STAGE(3)
SOL 7732-18-5 Water
CON 35 deg C, 8 atm

PRO L 75225-51-3
NTE reactant added in portions alternating with water over 2 h

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

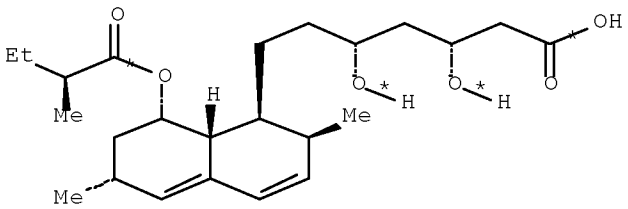
STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

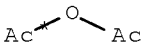
STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(11) OF 42 COMPOSED OF RX(3), RX(4)
RX(11) L + P ===> Q

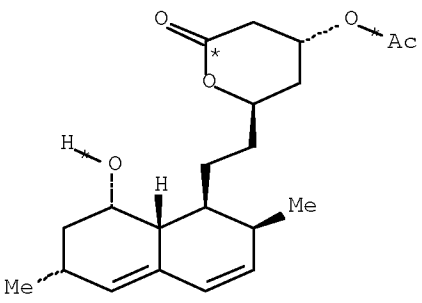


L



P

2
STEPS



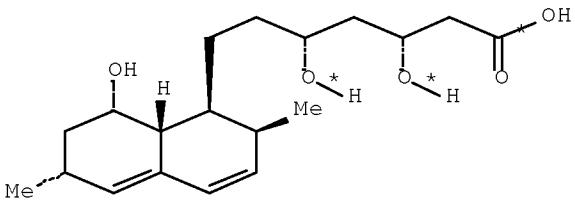
Q
YIELD 81%

```
RX(3)     RCT  L 75225-51-3

            STAGE(1)
               SOL  7732-18-5 Water
               CON  35 deg C

            STAGE(2)
               RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
               SOL  7732-18-5 Water
               CON  35 deg C

            STAGE(3)
               CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
               SOL  7732-18-5 Water
               CON  35 deg C

            STAGE(4)
               RGT  F 1336-21-6 NH4OH
               SOL  7732-18-5 Water
               CON  48 hours, 35 deg C, pH 9.5

            STAGE(5)
               RGT  O 7647-01-0 HCl
               SOL  7732-18-5 Water
               CON  pH 4.4

            STAGE(6)
               RGT  O 7647-01-0 HCl
               SOL  7732-18-5 Water
               CON  0.5 hours, pH 2.5

          PRO  N 132748-10-8
          NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
               SEQ ID NO:3)]; second and third stages buffer; fourth stage
               DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by
               HPLC

RX(4)     RCT  N 132748-10-8

            STAGE(1)
               SOL  75-09-2 CH2Cl2
               CON  room temperature

            STAGE(2)
               CAT  1122-58-3 4-DMAP
               CON  room temperature

            STAGE(3)
               RCT  P 108-24-7
               CON  8.5 hours, room temperature

            STAGE(4)
               CAT  1122-58-3 4-DMAP
               CON  11 hours, room temperature

            STAGE(5)
               SOL  7732-18-5 Water
```

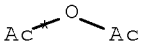
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

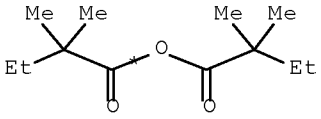
RX(12) OF 42 COMPOSED OF RX(4), RX(6)
RX(12) N + P + X ===> A



N

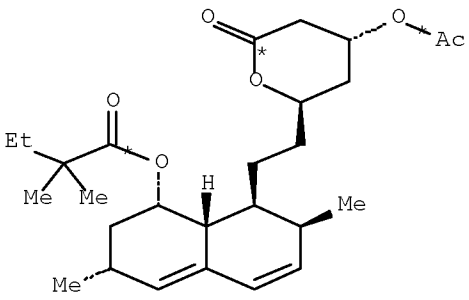


P



X

2
STEPS



A
YIELD 99%

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP

CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

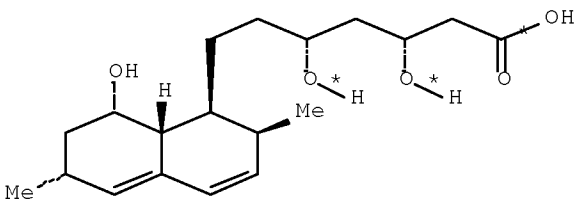
STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

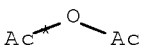
STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

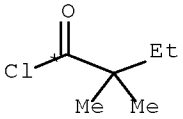
RX(13) OF 42 COMPOSED OF RX(4), RX(8)
RX(13) N + P + AC ===> A



N

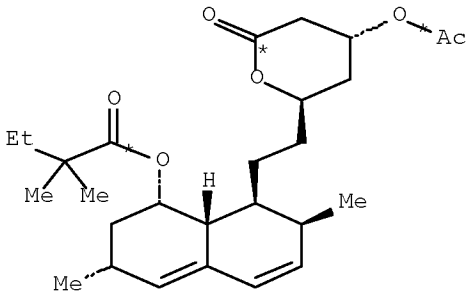


P



AC

2
STEPS
→



A
YIELD 97%

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(8) RCT Q 145576-24-5

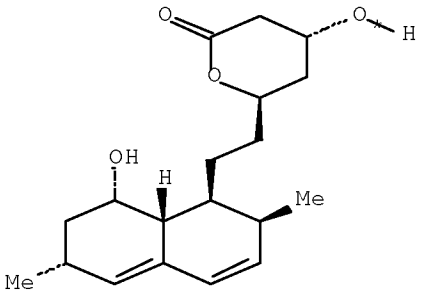
STAGE(1)
SOL 110-86-1 Pyridine

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 110-86-1 Pyridine

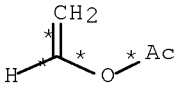
STAGE(3)
RCT AC 5856-77-9
SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

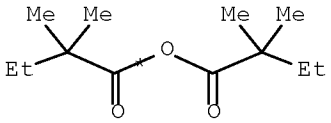
RX(14) OF 42 COMPOSED OF RX(5), RX(6)
RX(14) T + U + X ===> A



T

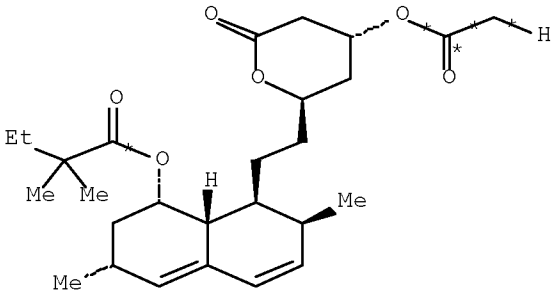


U



X

2
STEPS



A
YIELD 99%

RX(5) RCT T 79952-42-4, U 108-05-4
PRO Q 145576-24-5
CAT 9001-62-1 Lipase
SOL 1634-04-4 t-BuOMe
CON 44 hours, room temperature
NTE biotransformation, enzymic [lipase B (Candida antarctica)]

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

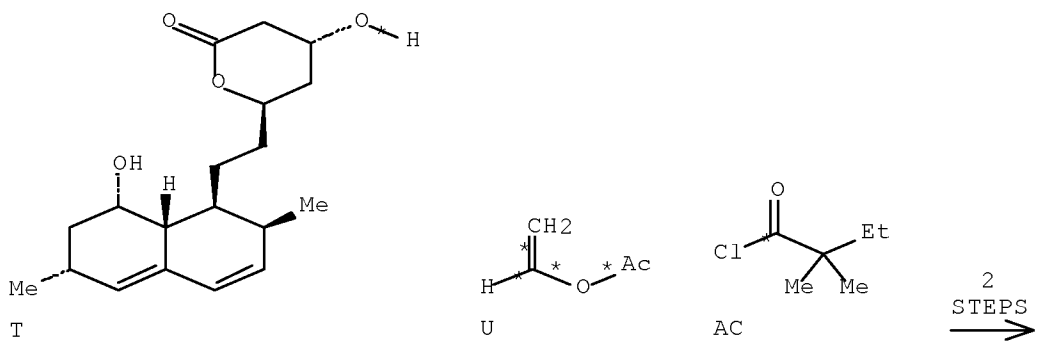
STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

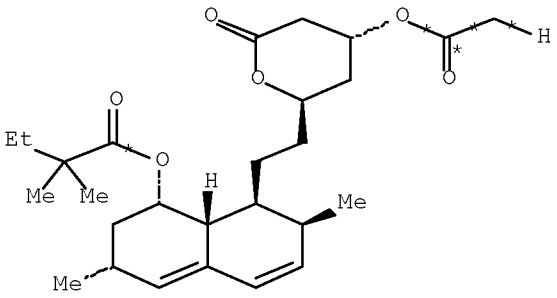
STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(15) OF 42 COMPOSED OF RX(5), RX(8)
RX(15) T + U + AC ===> A





A
YIELD 97%

RX(5) RCT T 79952-42-4, U 108-05-4
PRO Q 145576-24-5
CAT 9001-62-1 Lipase
SOL 1634-04-4 t-BuOMe
CON 44 hours, room temperature
NTE biotransformation, enzymic [lipase B (Candida antarctica)]

RX(8) RCT Q 145576-24-5

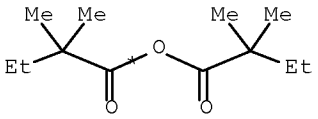
STAGE(1)
SOL 110-86-1 Pyridine

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 110-86-1 Pyridine

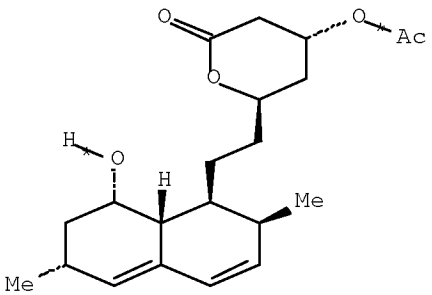
STAGE(3)
RCT AC 5856-77-9
SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

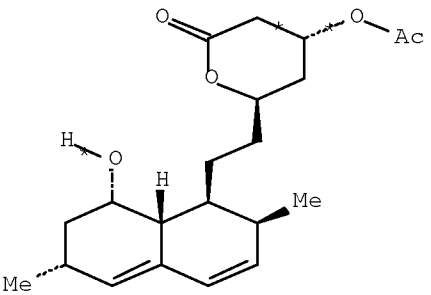
RX(16) OF 42 COMPOSED OF RX(6), RX(1)
RX(16) 3 X + 3 Q ===> B + C + D



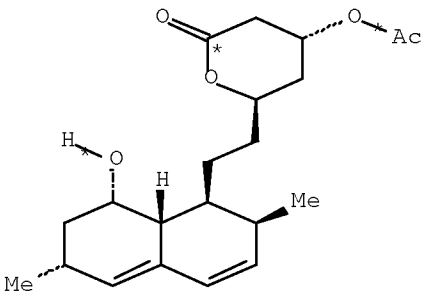
3 X



Q

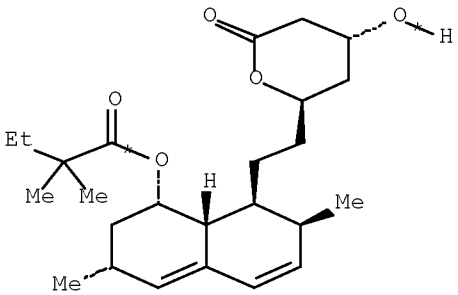


Q

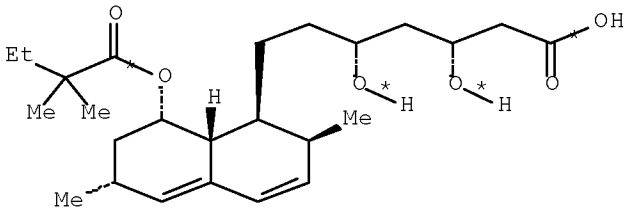


Q

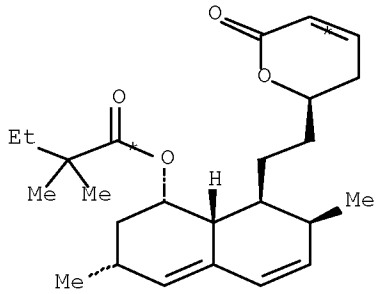
2
STEPS



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

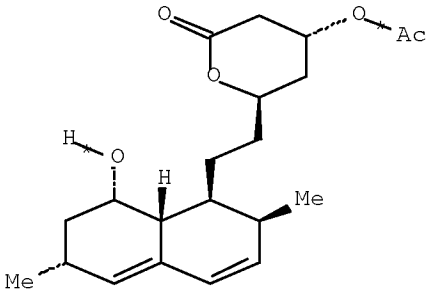
STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

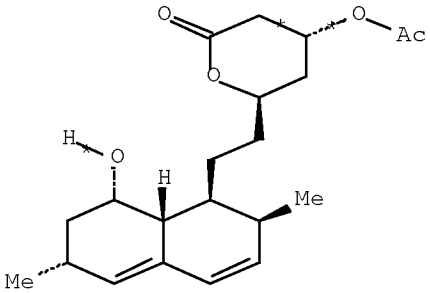
STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

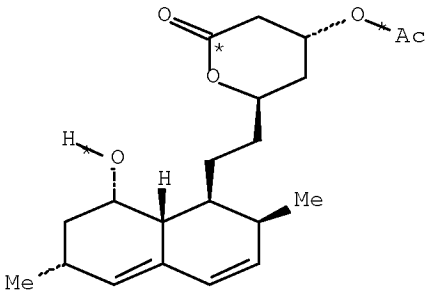
RX(17) OF 42 COMPOSED OF RX(8), RX(1)
RX(17) 3 Q + 3 AC ===> B + C + D



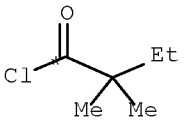
Q



Q

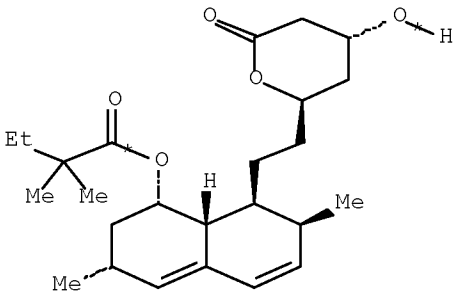


Q

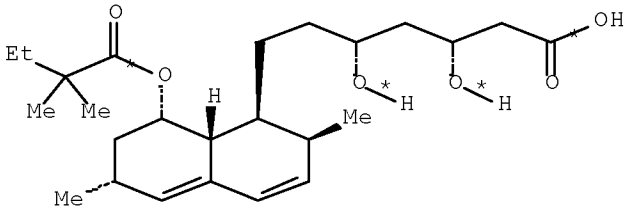


3 AC

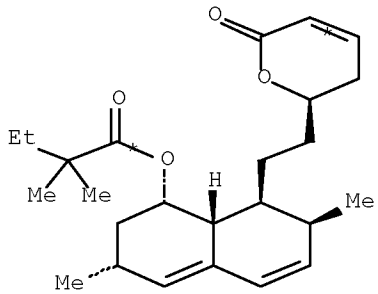
2 STEPS →



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(8) RCT Q 145576-24-5

STAGE(1)
SOL 110-86-1 Pyridine

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 110-86-1 Pyridine

STAGE(3)
RCT AC 5856-77-9
SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

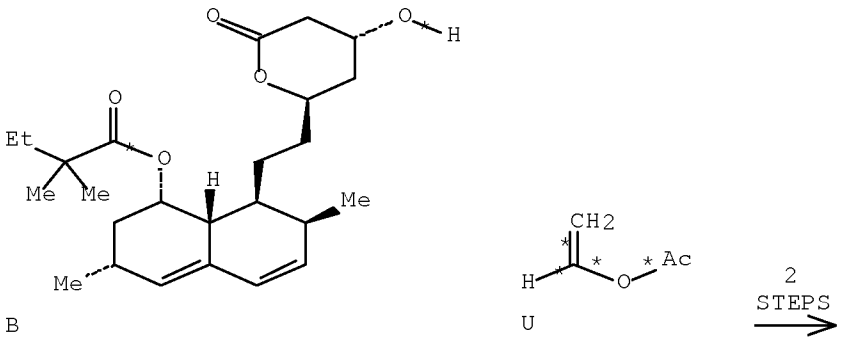
STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

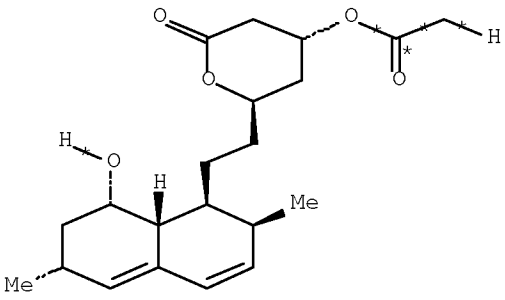
STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

RX(18) OF 42 COMPOSED OF RX(7), RX(5)
RX(18) B + U ===> Q



B U



Q
YIELD 60%

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

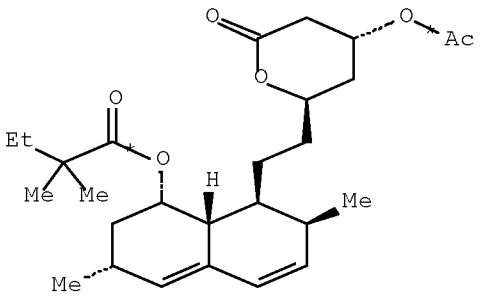
STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

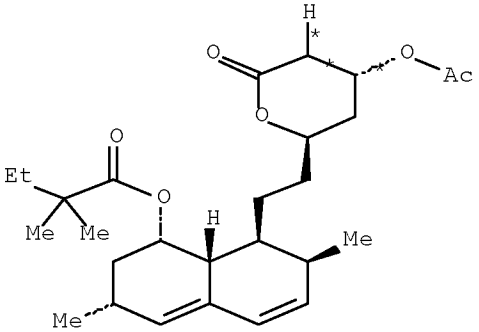
PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

RX(5) RCT T 79952-42-4, U 108-05-4
PRO Q 145576-24-5
CAT 9001-62-1 Lipase
SOL 1634-04-4 t-BuOMe
CON 44 hours, room temperature
NTE biotransformation, enzymic [lipase B (Candida antarctica)]

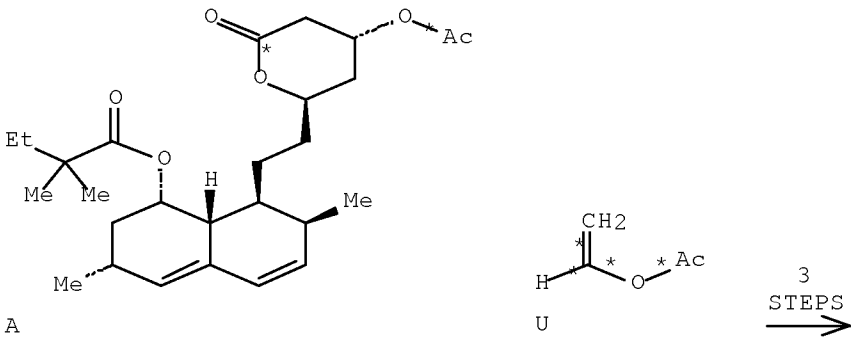
RX(19) OF 42 COMPOSED OF RX(1), RX(7), RX(5)
RX(19) 3 A + U ===> Q



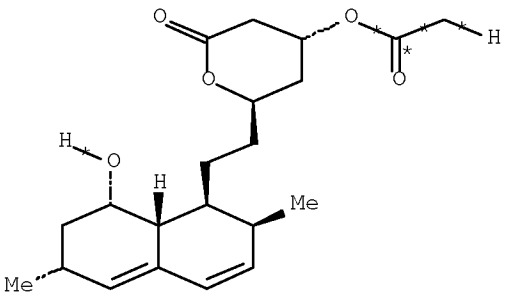
A



A



A U



Q
YIELD 60%

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip

STIRRER-PRO pH-stat system

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

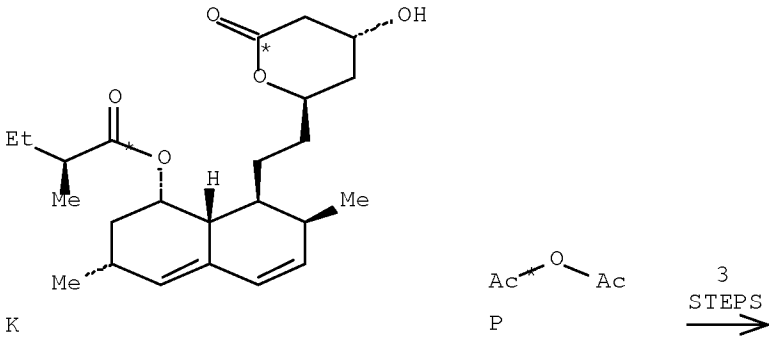
STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

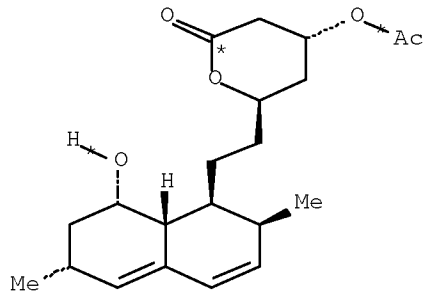
PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

RX(5) RCT T 79952-42-4, U 108-05-4
PRO Q 145576-24-5
CAT 9001-62-1 Lipase
SOL 1634-04-4 t-BuOMe
CON 44 hours, room temperature
NTE biotransformation, enzymic [lipase B (Candida antarctica)]

RX(20) OF 42 COMPOSED OF RX(2), RX(3), RX(4)
RX(20) K + P ===> Q



K P



YIELD 81%

RX(2)

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 35 deg C

STAGE(2)
RCT K 75330-75-5
CON 35 deg C

STAGE(3)
SOL 7732-18-5 Water
CON 35 deg C, 8 atm

PRO L 75225-51-3
NTE reactant added in portions alternating with water over 2 h

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water

CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

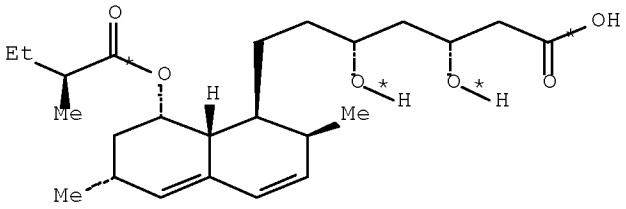
STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

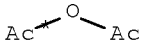
STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

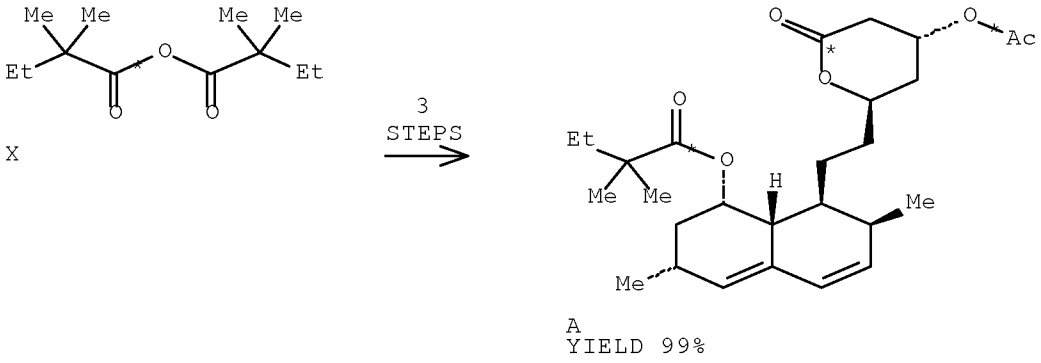
RX(21) OF 42 COMPOSED OF RX(3), RX(4), RX(6)
RX(21) L + P + X ===> A



L



P



A
YIELD 99%

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

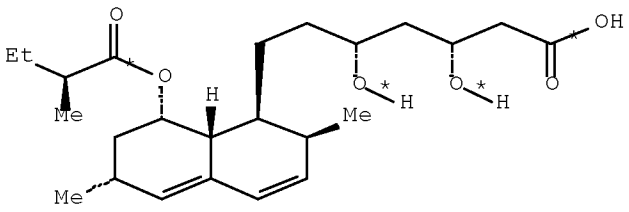
STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

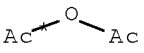
STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

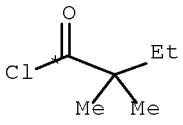
RX(22) OF 42 COMPOSED OF RX(3), RX(4), RX(8)
RX(22) L + P + AC ===> A



L

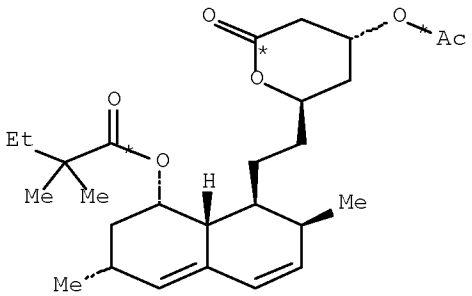


P



AC

3
STEPS
→



A
YIELD 97%

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(8) RCT Q 145576-24-5

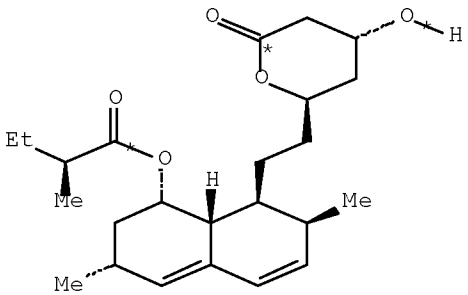
STAGE(1)
SOL 110-86-1 Pyridine

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 110-86-1 Pyridine

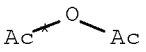
STAGE(3)
RCT AC 5856-77-9
SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

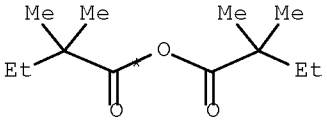
RX(23) OF 42 COMPOSED OF RX(2), RX(3), RX(4), RX(6)
RX(23) K + P + X ===> A



K

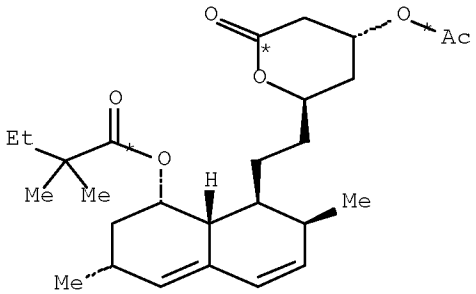


P



X

4
STEPS



A
YIELD 99%

RX(2)

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 35 deg C

STAGE(2)
RCT K 75330-75-5
CON 35 deg C

STAGE(3)
SOL 7732-18-5 Water
CON 35 deg C, 8 atm

PRO L 75225-51-3
NTE reactant added in portions alternating with water over 2 h

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2

SOL 75-05-8 MeCN
CON room temperature

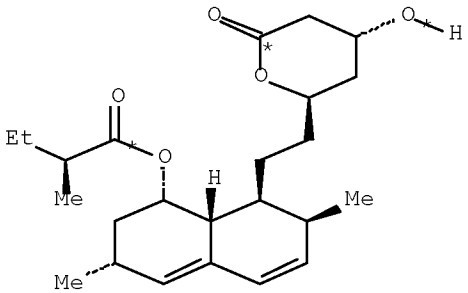
STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

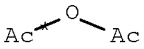
STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

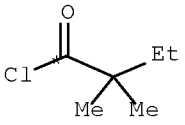
RX(24) OF 42 COMPOSED OF RX(2), RX(3), RX(4), RX(8)
RX(24) K + P + AC ===> A



K

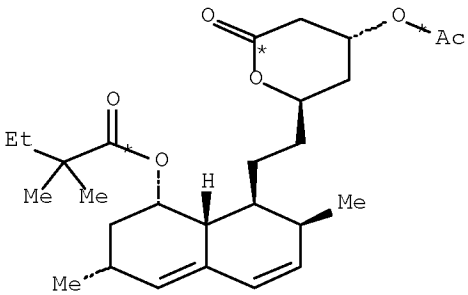


P



AC

4 STEPS →



A
YIELD 97%

RX(2)

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 35 deg C

STAGE(2)
RCT K 75330-75-5
CON 35 deg C

STAGE(3)
SOL 7732-18-5 Water
CON 35 deg C, 8 atm

PRO L 75225-51-3
NTE reactant added in portions alternating with water over 2 h

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2

CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(8) RCT Q 145576-24-5

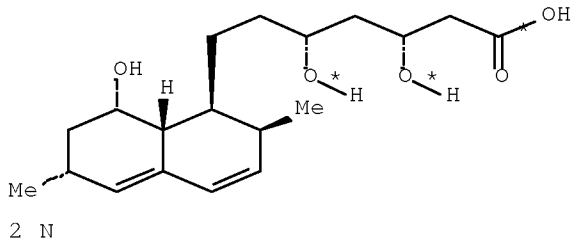
STAGE(1)
SOL 110-86-1 Pyridine

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 110-86-1 Pyridine

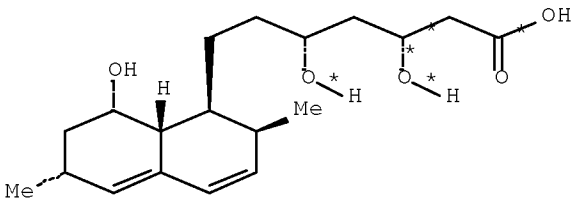
STAGE(3)
RCT AC 5856-77-9
SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

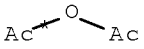
RX(25) OF 42 COMPOSED OF RX(4), RX(6), RX(1)
RX(25) 3 N + 3 P + 3 X ===> B + C + D



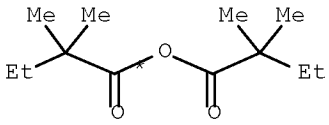
2 N



N

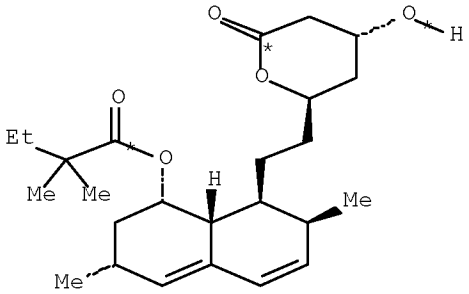


3 P

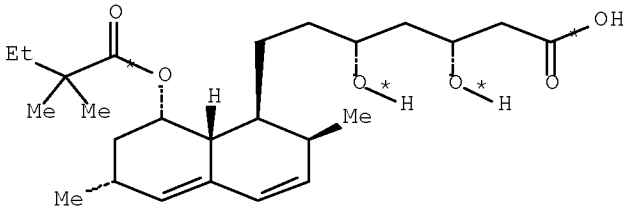


3 X

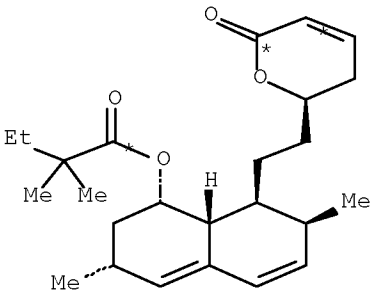
3
STEPS



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

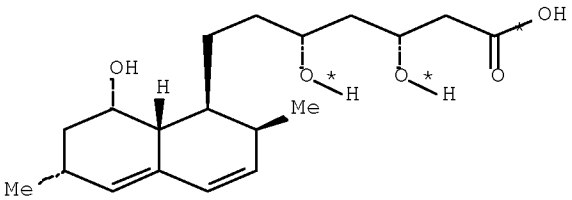
STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

```
            STAGE(3)
               RCT  P 108-24-7
               CON  8.5 hours, room temperature

            STAGE(4)
               CAT  1122-58-3 4-DMAP
               CON  11 hours, room temperature

            STAGE(5)
               SOL  7732-18-5 Water
               CON  room temperature

         PRO  Q 145576-24-5
         NTE  last stage quench; reaction monitored by HPLC

RX(6)

            STAGE(1)
               RGT  Y 34946-82-2 Cu(CF3SO3)2
               SOL  75-05-8 MeCN
               CON  room temperature

            STAGE(2)
               RCT  X 29138-64-5
               SOL  75-09-2 CH2Cl2
               CON  30 - 60 minutes, room temperature

            STAGE(3)
               RCT  Q 145576-24-5
               SOL  75-09-2 CH2Cl2
               CON  room temperature

            STAGE(4)
               SOL  7732-18-5 Water
               CON  room temperature

         PRO  A 145576-25-6
         NTE  reaction monitored by HPLC; third stage inverse addn.; last
              stage quench

RX(1)    RCT  A 145576-25-6

            STAGE(1)
               RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
               SOL  7732-18-5 Water, 67-56-1 MeOH
               CON  room temperature

            STAGE(2)
               CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
               SOL  7732-18-5 Water
               CON  room temperature

            STAGE(3)
               RGT  F 1336-21-6 NH4OH
               SOL  7732-18-5 Water
               CON  room temperature

            STAGE(4)
               SOL  108-88-3 PhMe
```

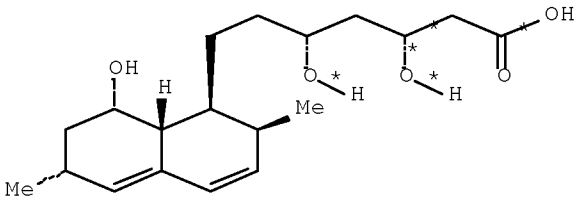
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

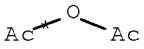
RX(26) OF 42 COMPOSED OF RX(4), RX(8), RX(1)
RX(26) 3 N + 3 P + 3 AC ===> B + C + D



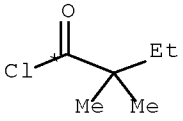
2 N



N

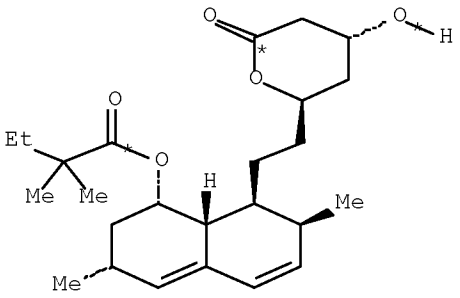


3 P

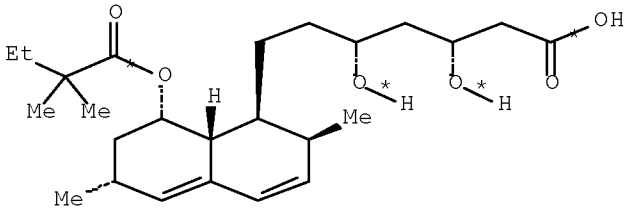


3 AC

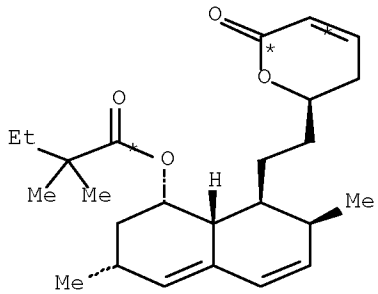
3 STEPS →



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

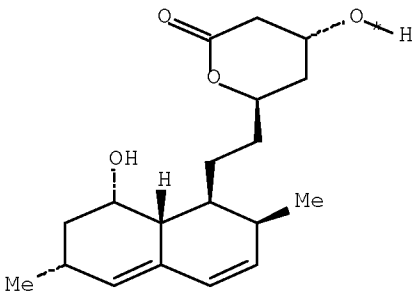
STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

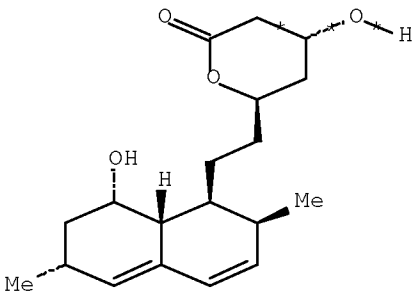
STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5

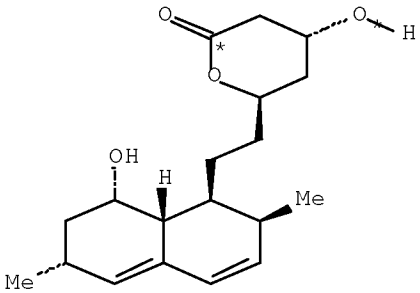
```
          NTE  last stage quench; reaction monitored by HPLC

RX(8)     RCT  Q 145576-24-5

             STAGE(1)
                SOL  110-86-1 Pyridine

             STAGE(2)
                CAT  1122-58-3 4-DMAP
                SOL  110-86-1 Pyridine

             STAGE(3)
                RCT  AC 5856-77-9
                SOL  110-86-1 Pyridine

          PRO  A 145576-25-6
          NTE  third stage syringe pump

RX(1)     RCT  A 145576-25-6

             STAGE(1)
                RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
                SOL  7732-18-5 Water, 67-56-1 MeOH
                CON  room temperature

             STAGE(2)
                CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
                SOL  7732-18-5 Water
                CON  room temperature

             STAGE(3)
                RGT  F 1336-21-6 NH4OH
                SOL  7732-18-5 Water
                CON  room temperature

             STAGE(4)
                SOL  108-88-3 PhMe
                CON  overnight, room temperature

          PRO  B 79902-63-9, C 121009-77-6, D 210980-68-0
          NTE  biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ
               ID NO:3)]; first three stages buffer; third stage DasGip
               STIRRER-PRO pH-stat system


RX(27) OF 42 COMPOSED OF RX(5), RX(6), RX(1)
RX(27)    3 T  +  3 U  +  3 X  ===>  B  +  C  +  D
```



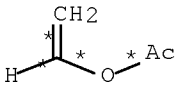
T



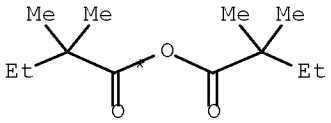
T



T

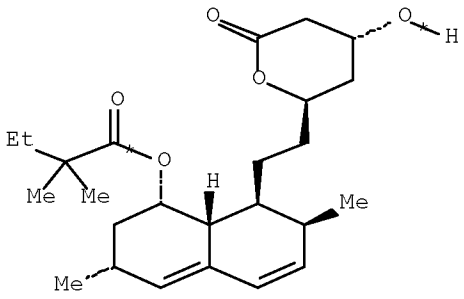


3 U

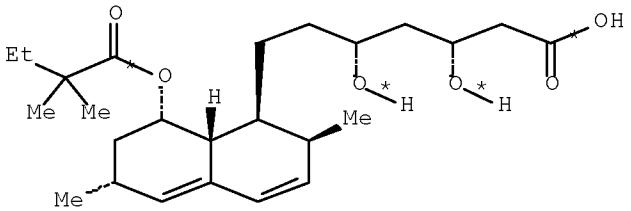


3 X

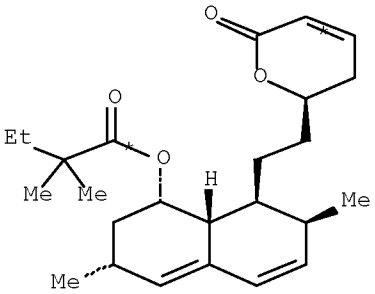
3
STEPS



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(5) RCT T 79952-42-4, U 108-05-4
PRO Q 145576-24-5
CAT 9001-62-1 Lipase
SOL 1634-04-4 t-BuOMe
CON 44 hours, room temperature
NTE biotransformation, enzymic [lipase B (Candida antarctica)]

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water

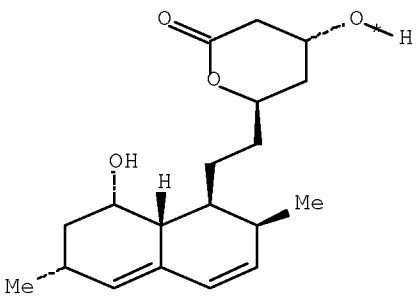
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

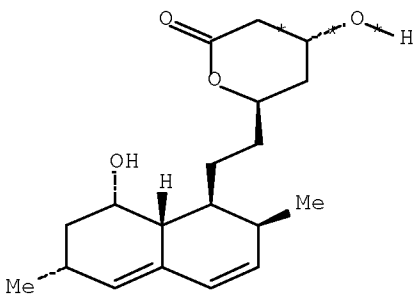
STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

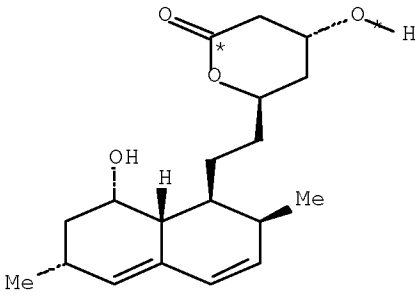
RX(28) OF 42 COMPOSED OF RX(5), RX(8), RX(1)
RX(28) 3 T + 3 U + 3 AC ===> B + C + D



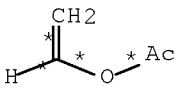
T



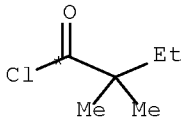
T



T

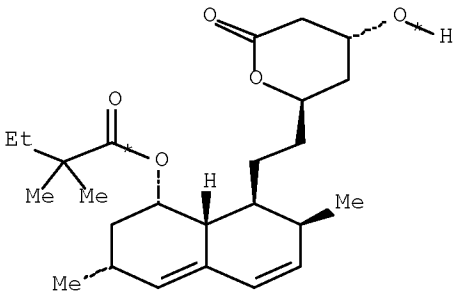


3 U

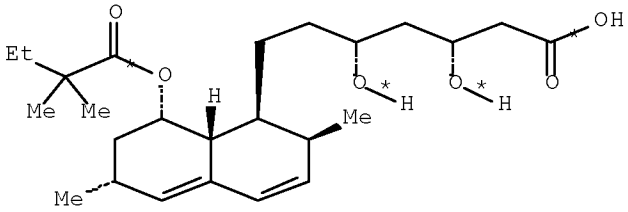


3 AC

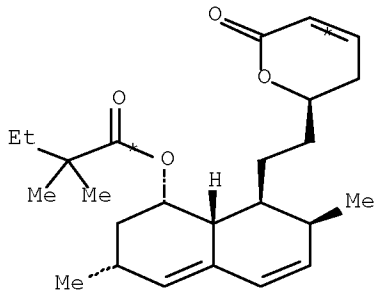
3 STEPS



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(5) RCT T 79952-42-4, U 108-05-4
PRO Q 145576-24-5
CAT 9001-62-1 Lipase
SOL 1634-04-4 t-BuOMe
CON 44 hours, room temperature
NTE biotransformation, enzymic [lipase B (Candida antarctica)]

RX(8) RCT Q 145576-24-5

STAGE(1)
SOL 110-86-1 Pyridine

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 110-86-1 Pyridine

STAGE(3)
RCT AC 5856-77-9
SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

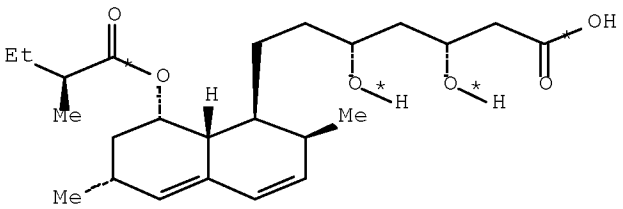
STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

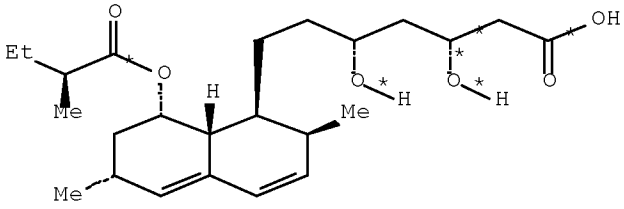
STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

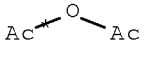
RX(29) OF 42 COMPOSED OF RX(3), RX(4), RX(6), RX(1)
RX(29) 3 L + 3 P + 3 X ===> 3 B + C + D



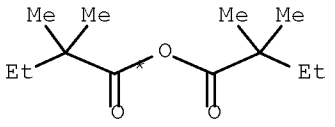
2 L



L

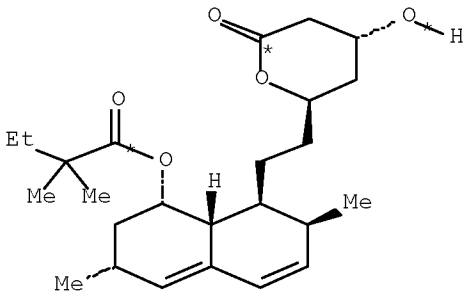


3 P

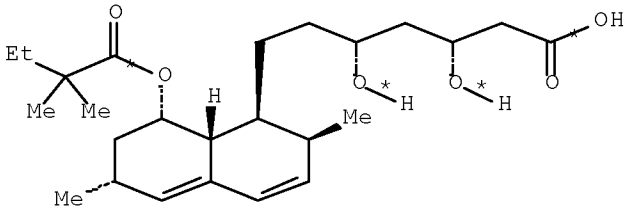


3 X

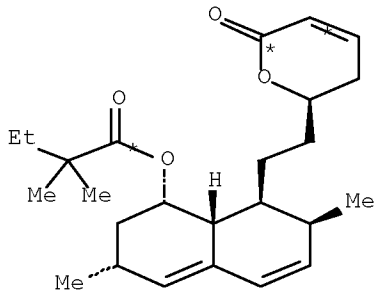
4
STEPS



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl

SOL 7732-18-5 Water
CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

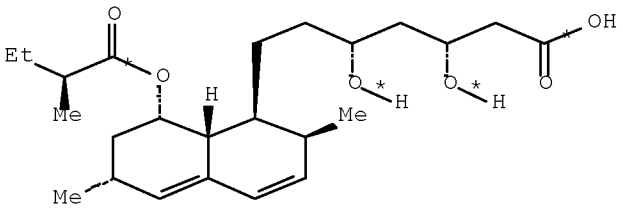
STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

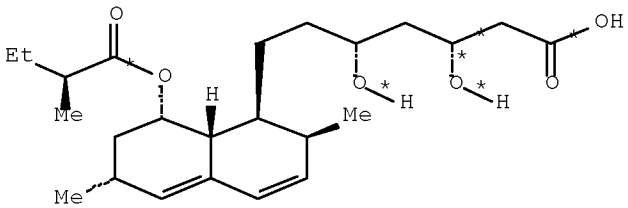
STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

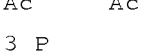
RX(30) OF 42 COMPOSED OF RX(3), RX(4), RX(8), RX(1)
RX(30) 3 L + 3 P + 3 AC ===> B + C + D



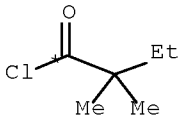
2 L



L

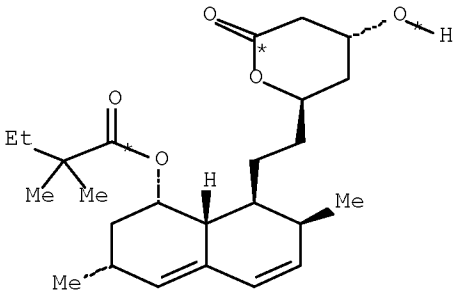


3 P

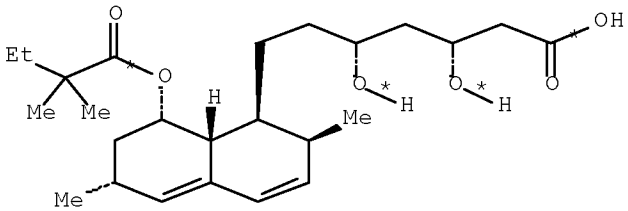


3 AC

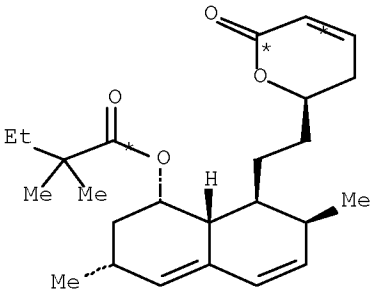
4
STEPS



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein

```
                SOL  7732-18-5 Water
                CON  35 deg C

             STAGE(4)
                RGT  F 1336-21-6 NH4OH
                SOL  7732-18-5 Water
                CON  48 hours, 35 deg C, pH 9.5

             STAGE(5)
                RGT  O 7647-01-0 HCl
                SOL  7732-18-5 Water
                CON  pH 4.4

             STAGE(6)
                RGT  O 7647-01-0 HCl
                SOL  7732-18-5 Water
                CON  0.5 hours, pH 2.5

          PRO  N 132748-10-8
          NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
               SEQ ID NO:3)]; second and third stages buffer; fourth stage
               DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by
               HPLC

RX(4)     RCT  N 132748-10-8

             STAGE(1)
                SOL  75-09-2 CH2Cl2
                CON  room temperature

             STAGE(2)
                CAT  1122-58-3 4-DMAP
                CON  room temperature

             STAGE(3)
                RCT  P 108-24-7
                CON  8.5 hours, room temperature

             STAGE(4)
                CAT  1122-58-3 4-DMAP
                CON  11 hours, room temperature

             STAGE(5)
                SOL  7732-18-5 Water
                CON  room temperature

          PRO  Q 145576-24-5
          NTE  last stage quench; reaction monitored by HPLC

RX(8)     RCT  Q 145576-24-5

             STAGE(1)
                SOL  110-86-1 Pyridine

             STAGE(2)
                CAT  1122-58-3 4-DMAP
                SOL  110-86-1 Pyridine

             STAGE(3)
                RCT  AC 5856-77-9
```

SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

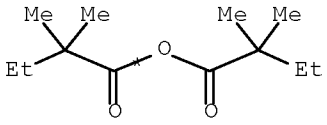
STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

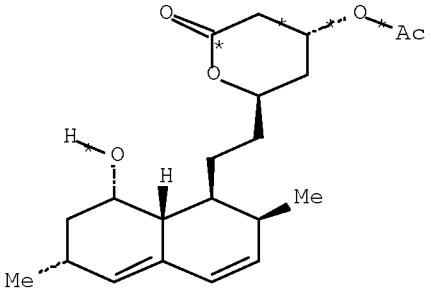
STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

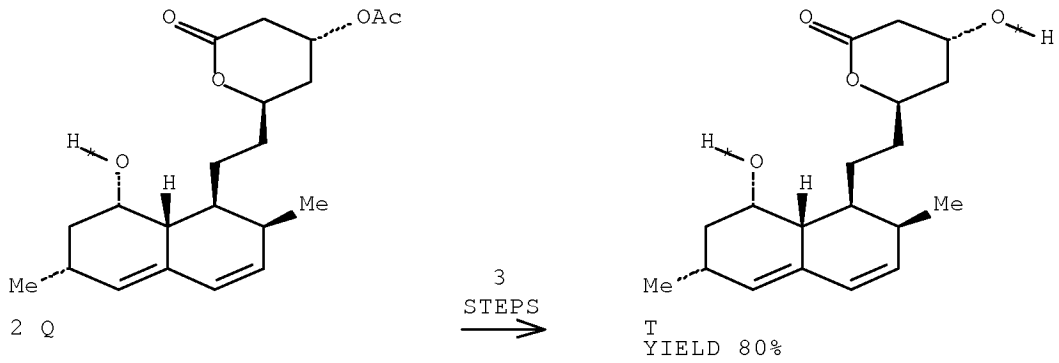
RX(31) OF 42 COMPOSED OF RX(6), RX(1), RX(7)
RX(31) 3 X + 3 Q ===> T



3 X



Q



RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

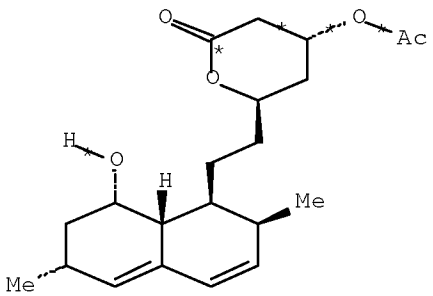
STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

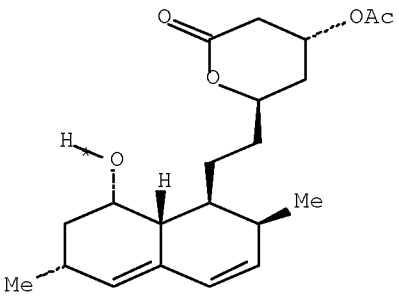
STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

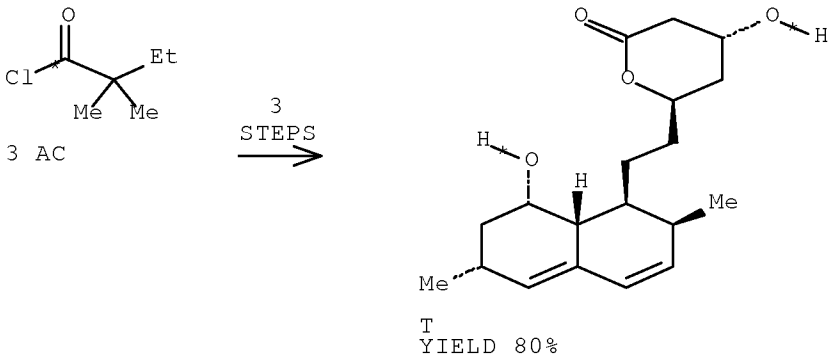
RX(32) OF 42 COMPOSED OF RX(8), RX(1), RX(7)
RX(32) 3 Q + 3 AC ===> T



Q



2 Q



T
YIELD 80%

RX(8) RCT Q 145576-24-5

STAGE(1)
SOL 110-86-1 Pyridine

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 110-86-1 Pyridine

STAGE(3)
RCT AC 5856-77-9
SOL 110-86-1 Pyridine

PRO A 145576-25-6
NTE third stage syringe pump

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

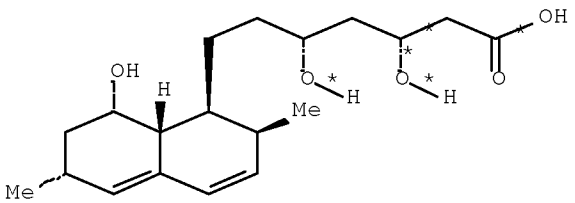
STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

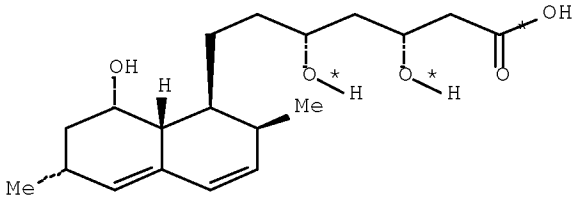
STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

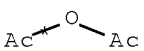
RX(33) OF 42 COMPOSED OF RX(4), RX(6), RX(1), RX(7)
RX(33) 3 N + 3 P + 3 X ===> T



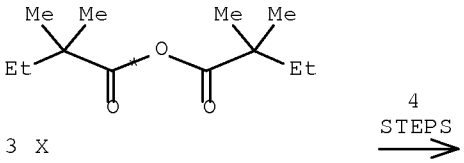
N



2 N

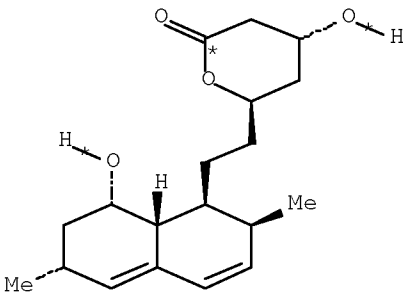


3 P



3 X

4
STEPS



T
YIELD 80%

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

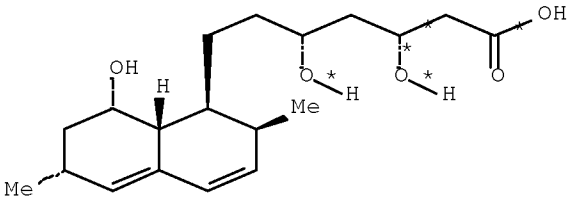
STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

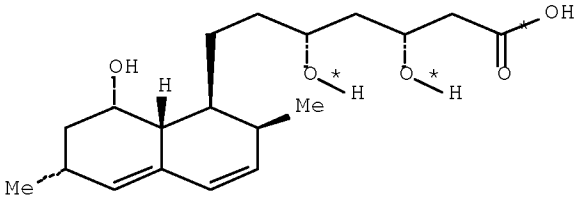
STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

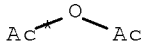
RX(34) OF 42 COMPOSED OF RX(4), RX(8), RX(1), RX(7)
RX(34) 3 N + 3 P + 3 AC ===> T



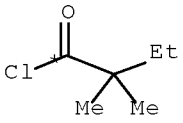
N



2 N

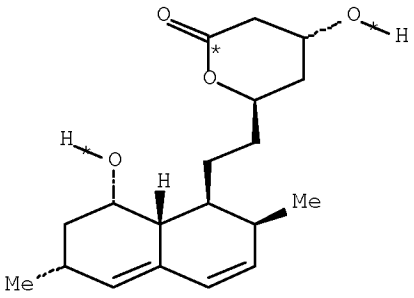


3 P



3 AC

4
STEPS



T
YIELD 80%

```
RX(4)      RCT  N 132748-10-8

             STAGE(1)
                SOL  75-09-2 CH2Cl2
                CON  room temperature

             STAGE(2)
                CAT  1122-58-3 4-DMAP
                CON  room temperature

             STAGE(3)
                RCT  P 108-24-7
                CON  8.5 hours, room temperature

             STAGE(4)
                CAT  1122-58-3 4-DMAP
                CON  11 hours, room temperature

             STAGE(5)
                SOL  7732-18-5 Water
                CON  room temperature

           PRO  Q 145576-24-5
           NTE  last stage quench; reaction monitored by HPLC

RX(8)      RCT  Q 145576-24-5

             STAGE(1)
                SOL  110-86-1 Pyridine

             STAGE(2)
                CAT  1122-58-3 4-DMAP
                SOL  110-86-1 Pyridine

             STAGE(3)
                RCT  AC 5856-77-9
                SOL  110-86-1 Pyridine

           PRO  A 145576-25-6
           NTE  third stage syringe pump

RX(1)      RCT  A 145576-25-6

             STAGE(1)
                RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
                SOL  7732-18-5 Water, 67-56-1 MeOH
                CON  room temperature

             STAGE(2)
                CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
                SOL  7732-18-5 Water
                CON  room temperature

             STAGE(3)
                RGT  F 1336-21-6 NH4OH
                SOL  7732-18-5 Water
                CON  room temperature

             STAGE(4)
                SOL  108-88-3 PhMe
```

CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

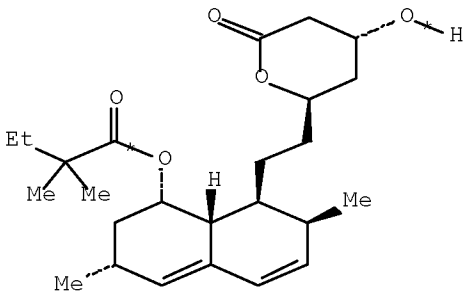
STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

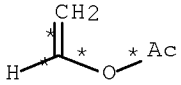
STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

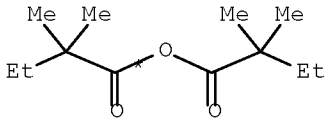
RX(35) OF 42 COMPOSED OF RX(7), RX(5), RX(6)
RX(35) B + U + X ===> A



B

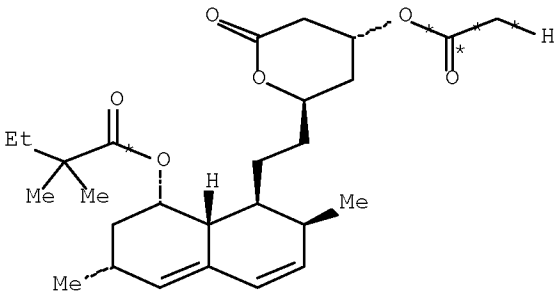


U



X

3
STEPS



A
YIELD 99%

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

RX(5) RCT T 79952-42-4, U 108-05-4
PRO Q 145576-24-5
CAT 9001-62-1 Lipase
SOL 1634-04-4 t-BuOMe
CON 44 hours, room temperature
NTE biotransformation, enzymic [lipase B (Candida antarctica)]

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2

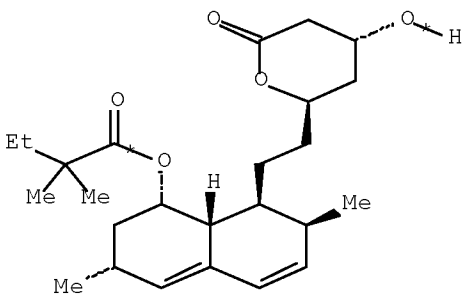
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

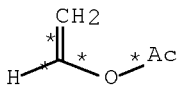
STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

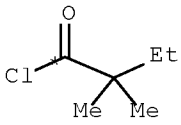
RX(36) OF 42 COMPOSED OF RX(7), RX(5), RX(8)
RX(36) B + U + AC ===> A



B

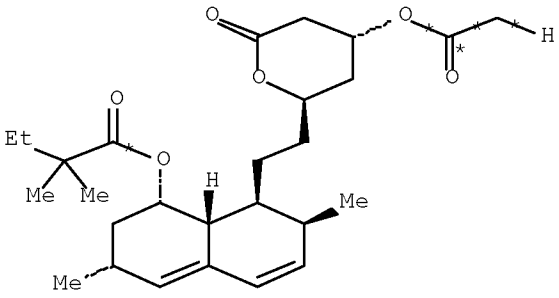


U



AC

3 STEPS

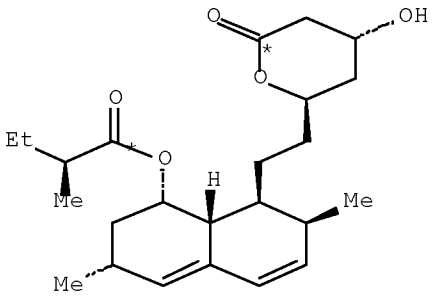


A
YIELD 97%

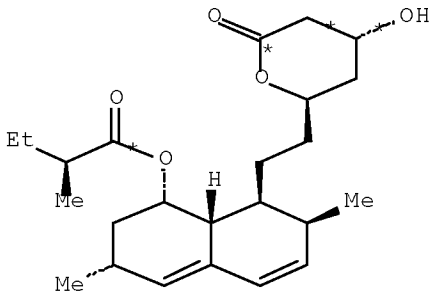
RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein

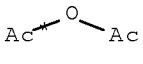
```
                SOL  7732-18-5 Water, 67-56-1 MeOH

              STAGE(2)
                RGT  F 1336-21-6 NH4OH
                SOL  7732-18-5 Water
                CON  48 hours, pH 9 - 9.5

              STAGE(3)
                RGT  AA 13968-08-6 Hydronium (H3O+)
                SOL  7732-18-5 Water
                CON  pH 2

              STAGE(4)
                SOL  108-21-4 Acetic acid, 1-methylethyl ester
                CON  reflux

            PRO  T 79952-42-4
            NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
                 SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark
                 trap

RX(5)       RCT  T 79952-42-4, U 108-05-4
            PRO  Q 145576-24-5
            CAT  9001-62-1 Lipase
            SOL  1634-04-4 t-BuOMe
            CON  44 hours, room temperature
            NTE  biotransformation, enzymic [lipase B (Candida antarctica)]

RX(8)       RCT  Q 145576-24-5

              STAGE(1)
                SOL  110-86-1 Pyridine

              STAGE(2)
                CAT  1122-58-3 4-DMAP
                SOL  110-86-1 Pyridine

              STAGE(3)
                RCT  AC 5856-77-9
                SOL  110-86-1 Pyridine

            PRO  A 145576-25-6
            NTE  third stage syringe pump


RX(37) OF 42 COMPOSED OF RX(2), RX(3), RX(4), RX(6), RX(1)
RX(37)    3 K  +  3 P  +  3 X  ===>  B  +  C  +  D
```



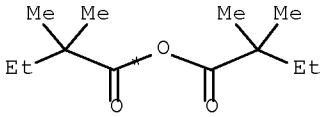
2 K



K

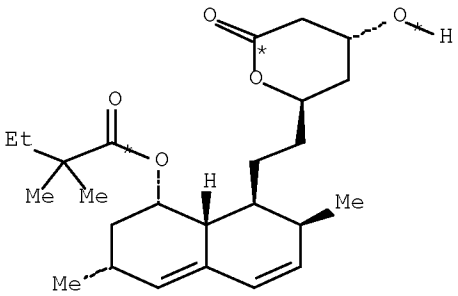


3 P

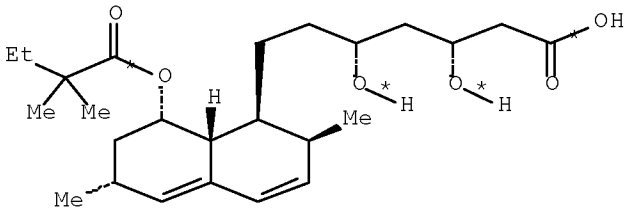


3 X

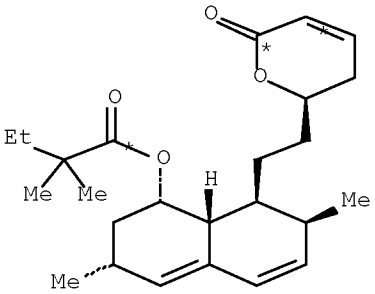
5
STEPS



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(2)

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 35 deg C

STAGE(2)
RCT K 75330-75-5
CON 35 deg C

STAGE(3)
SOL 7732-18-5 Water
CON 35 deg C, 8 atm

PRO L 75225-51-3
NTE reactant added in portions alternating with water over 2 h

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water

```
          CON  pH 4.4

        STAGE(6)
          RGT  O 7647-01-0 HCl
          SOL  7732-18-5 Water
          CON  0.5 hours, pH 2.5

      PRO  N 132748-10-8
      NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
           SEQ ID NO:3)]; second and third stages buffer; fourth stage
           DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by
           HPLC

RX(4) RCT  N 132748-10-8

        STAGE(1)
          SOL  75-09-2 CH2Cl2
          CON  room temperature

        STAGE(2)
          CAT  1122-58-3 4-DMAP
          CON  room temperature

        STAGE(3)
          RCT  P 108-24-7
          CON  8.5 hours, room temperature

        STAGE(4)
          CAT  1122-58-3 4-DMAP
          CON  11 hours, room temperature

        STAGE(5)
          SOL  7732-18-5 Water
          CON  room temperature

      PRO  Q 145576-24-5
      NTE  last stage quench; reaction monitored by HPLC

RX(6)

        STAGE(1)
          RGT  Y 34946-82-2 Cu(CF3SO3)2
          SOL  75-05-8 MeCN
          CON  room temperature

        STAGE(2)
          RCT  X 29138-64-5
          SOL  75-09-2 CH2Cl2
          CON  30 - 60 minutes, room temperature

        STAGE(3)
          RCT  Q 145576-24-5
          SOL  75-09-2 CH2Cl2
          CON  room temperature

        STAGE(4)
          SOL  7732-18-5 Water
          CON  room temperature

      PRO  A 145576-25-6
```

NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

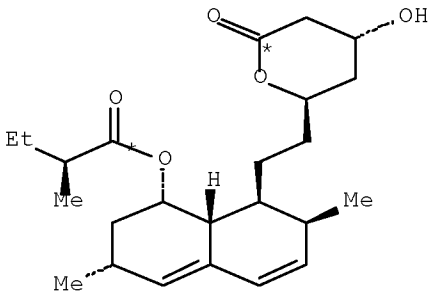
STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

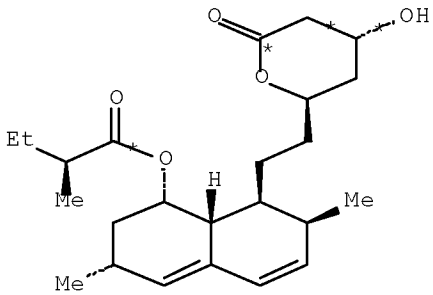
STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

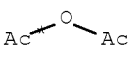
RX(38) OF 42 COMPOSED OF RX(2), RX(3), RX(4), RX(8), RX(1)
RX(38) 3 K + 3 P + 3 AC ===> B + C + D



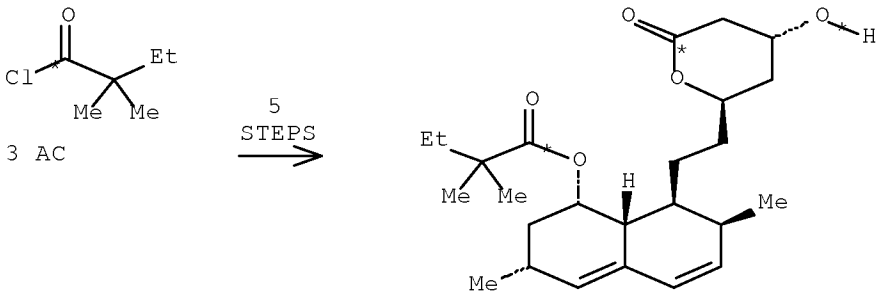
2 K



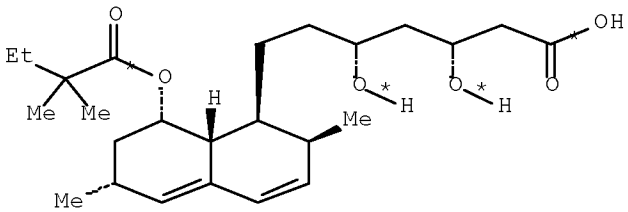
K



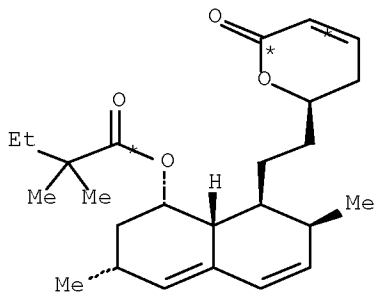
3 P



B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(2)

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 35 deg C

STAGE(2)
RCT K 75330-75-5
CON 35 deg C

STAGE(3)
SOL 7732-18-5 Water
CON 35 deg C, 8 atm

PRO L 75225-51-3
NTE reactant added in portions alternating with water over 2 h

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

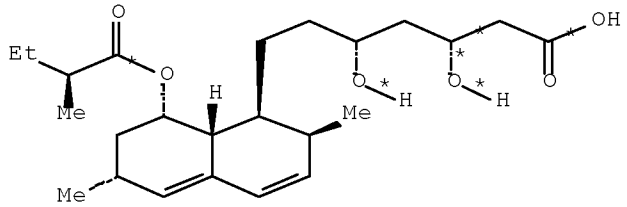
STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

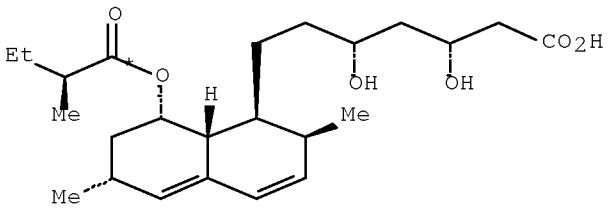
RX(8) RCT Q 145576-24-5

STAGE(1)

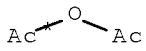
```
                SOL  110-86-1 Pyridine

              STAGE(2)
                CAT  1122-58-3 4-DMAP
                SOL  110-86-1 Pyridine

              STAGE(3)
                RCT  AC 5856-77-9
                SOL  110-86-1 Pyridine

            PRO  A 145576-25-6
            NTE  third stage syringe pump

RX(1)       RCT  A 145576-25-6

              STAGE(1)
                RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
                SOL  7732-18-5 Water, 67-56-1 MeOH
                CON  room temperature

              STAGE(2)
                CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
                SOL  7732-18-5 Water
                CON  room temperature

              STAGE(3)
                RGT  F 1336-21-6 NH4OH
                SOL  7732-18-5 Water
                CON  room temperature

              STAGE(4)
                SOL  108-88-3 PhMe
                CON  overnight, room temperature

            PRO  B 79902-63-9, C 121009-77-6, D 210980-68-0
            NTE  biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ
                 ID NO:3)]; first three stages buffer; third stage DasGip
                 STIRRER-PRO pH-stat system


RX(39) OF 42 COMPOSED OF RX(3), RX(4), RX(6), RX(1), RX(7)
RX(39)    3 L  +  3 P  +  3 X  ===>  T
```



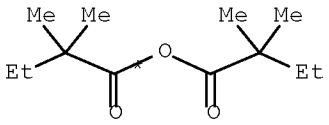
L



2 L

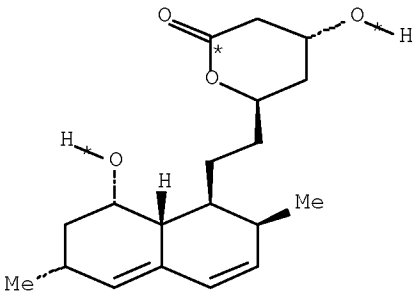


3 P



3 X

5
STEPS



T
YIELD 80%

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl

SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

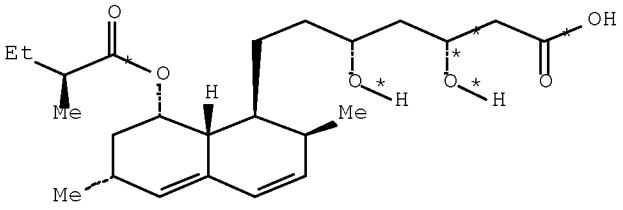
STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(4)
SOL 7732-18-5 Water
CON room temperature

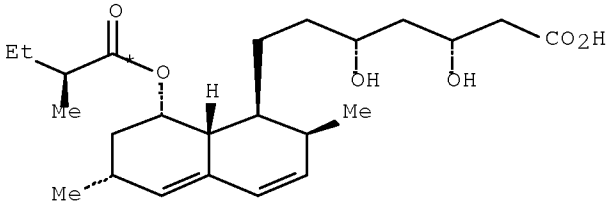
PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(1) RCT A 145576-25-6

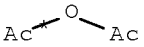
```
            STAGE(1)
               RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
               SOL  7732-18-5 Water, 67-56-1 MeOH
               CON  room temperature

            STAGE(2)
               CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
               SOL  7732-18-5 Water
               CON  room temperature

            STAGE(3)
               RGT  F 1336-21-6 NH4OH
               SOL  7732-18-5 Water
               CON  room temperature

            STAGE(4)
               SOL  108-88-3 PhMe
               CON  overnight, room temperature

          PRO  B 79902-63-9, C 121009-77-6, D 210980-68-0
          NTE  biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ
               ID NO:3)]; first three stages buffer; third stage DasGip
               STIRRER-PRO pH-stat system

RX(7)     RCT  B 79902-63-9

            STAGE(1)
               CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
               SOL  7732-18-5 Water, 67-56-1 MeOH

            STAGE(2)
               RGT  F 1336-21-6 NH4OH
               SOL  7732-18-5 Water
               CON  48 hours, pH 9 - 9.5

            STAGE(3)
               RGT  AA 13968-08-6 Hydronium (H3O+)
               SOL  7732-18-5 Water
               CON  pH 2

            STAGE(4)
               SOL  108-21-4 Acetic acid, 1-methylethyl ester
               CON  reflux

          PRO  T 79952-42-4
          NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
               SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark
               trap


RX(40) OF 42 COMPOSED OF RX(3), RX(4), RX(8), RX(1), RX(7)
RX(40)    3 L  +  3 P  +  3 AC  ===>  T
```



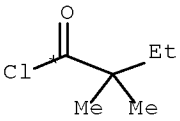
L



2 L

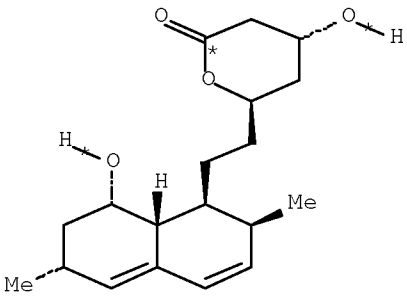


3 P



3 AC

5
STEPS



T
YIELD 80%

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 4.4

STAGE(6)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, pH 2.5

PRO N 132748-10-8
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; second and third stages buffer; fourth stage DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by HPLC

RX(4) RCT N 132748-10-8

STAGE(1)
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(2)
CAT 1122-58-3 4-DMAP
CON room temperature

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

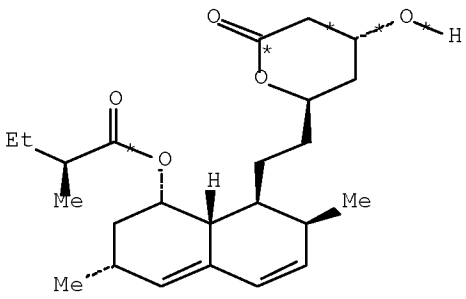
RX(8) RCT Q 145576-24-5

STAGE(1)
SOL 110-86-1 Pyridine

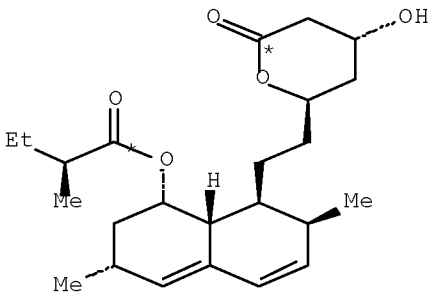
```
            STAGE(2)
               CAT  1122-58-3 4-DMAP
               SOL  110-86-1 Pyridine

            STAGE(3)
               RCT  AC 5856-77-9
               SOL  110-86-1 Pyridine

         PRO  A 145576-25-6
         NTE  third stage syringe pump

RX(1)    RCT  A 145576-25-6

            STAGE(1)
               RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
               SOL  7732-18-5 Water, 67-56-1 MeOH
               CON  room temperature

            STAGE(2)
               CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
               SOL  7732-18-5 Water
               CON  room temperature

            STAGE(3)
               RGT  F 1336-21-6 NH4OH
               SOL  7732-18-5 Water
               CON  room temperature

            STAGE(4)
               SOL  108-88-3 PhMe
               CON  overnight, room temperature

         PRO  B 79902-63-9, C 121009-77-6, D 210980-68-0
         NTE  biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ
              ID NO:3)]; first three stages buffer; third stage DasGip
              STIRRER-PRO pH-stat system

RX(7)    RCT  B 79902-63-9

            STAGE(1)
               CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
               SOL  7732-18-5 Water, 67-56-1 MeOH

            STAGE(2)
               RGT  F 1336-21-6 NH4OH
               SOL  7732-18-5 Water
               CON  48 hours, pH 9 - 9.5

            STAGE(3)
               RGT  AA 13968-08-6 Hydronium (H3O+)
               SOL  7732-18-5 Water
               CON  pH 2

            STAGE(4)
               SOL  108-21-4 Acetic acid, 1-methylethyl ester
               CON  reflux

         PRO  T 79952-42-4
         NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
```

SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

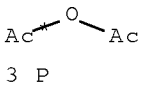
RX(41) OF 42 COMPOSED OF RX(2), RX(3), RX(4), RX(6), RX(1), RX(7)
RX(41) 3 K + 3 P + 3 X ===> T



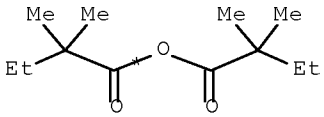
K



2 K

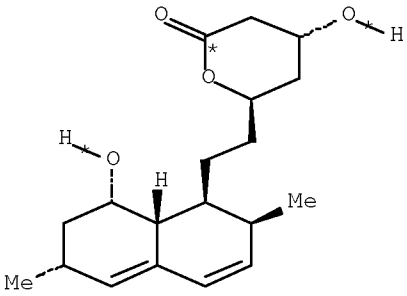


3 P



3 X

6 STEPS



T
YIELD 80%

RX(2)

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH

```
                CON  35 deg C

              STAGE(2)
                RCT  K 75330-75-5
                CON  35 deg C

              STAGE(3)
                SOL  7732-18-5 Water
                CON  35 deg C, 8 atm

            PRO  L 75225-51-3
            NTE  reactant added in portions alternating with water over 2 h

RX(3)       RCT  L 75225-51-3

              STAGE(1)
                SOL  7732-18-5 Water
                CON  35 deg C

              STAGE(2)
                RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
                SOL  7732-18-5 Water
                CON  35 deg C

              STAGE(3)
                CAT  851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
                SOL  7732-18-5 Water
                CON  35 deg C

              STAGE(4)
                RGT  F 1336-21-6 NH4OH
                SOL  7732-18-5 Water
                CON  48 hours, 35 deg C, pH 9.5

              STAGE(5)
                RGT  O 7647-01-0 HCl
                SOL  7732-18-5 Water
                CON  pH 4.4

              STAGE(6)
                RGT  O 7647-01-0 HCl
                SOL  7732-18-5 Water
                CON  0.5 hours, pH 2.5

            PRO  N 132748-10-8
            NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
                 SEQ ID NO:3)]; second and third stages buffer; fourth stage
                 DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by
                 HPLC

RX(4)       RCT  N 132748-10-8

              STAGE(1)
                SOL  75-09-2 CH2Cl2
                CON  room temperature

              STAGE(2)
                CAT  1122-58-3 4-DMAP
                CON  room temperature
```

STAGE(3)
RCT P 108-24-7
CON 8.5 hours, room temperature

STAGE(4)
CAT 1122-58-3 4-DMAP
CON 11 hours, room temperature

STAGE(5)
SOL 7732-18-5 Water
CON room temperature

PRO Q 145576-24-5
NTE last stage quench; reaction monitored by HPLC

RX(6)

STAGE(1)
RGT Y 34946-82-2 Cu(CF3SO3)2
SOL 75-05-8 MeCN
CON room temperature

STAGE(2)
RCT X 29138-64-5
SOL 75-09-2 CH2Cl2
CON 30 - 60 minutes, room temperature

STAGE(3)
RCT Q 145576-24-5
SOL 75-09-2 CH2Cl2
CON room temperature

STAGE(4)
SOL 7732-18-5 Water
CON room temperature

PRO A 145576-25-6
NTE reaction monitored by HPLC; third stage inverse addn.; last stage quench

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

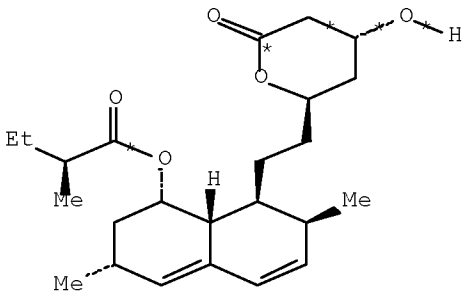
STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

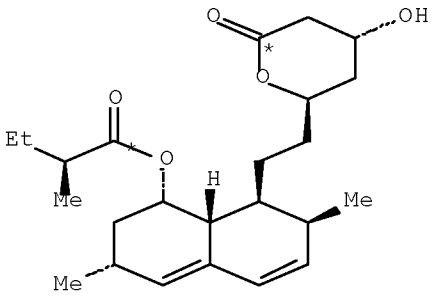
STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

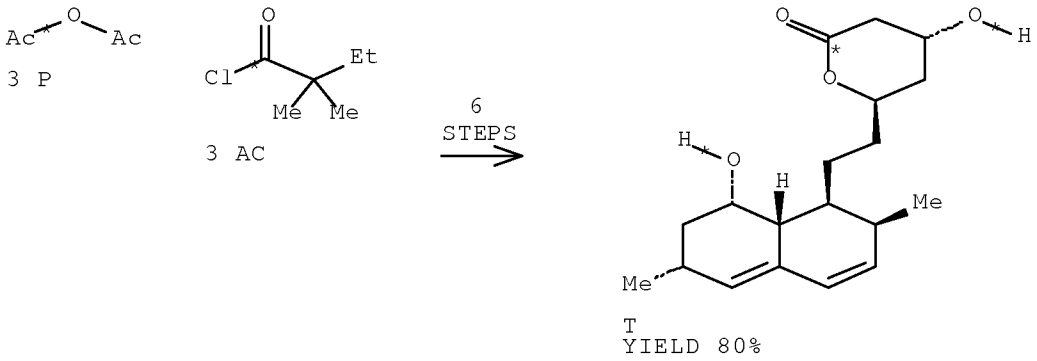
RX(42) OF 42 COMPOSED OF RX(2), RX(3), RX(4), RX(8), RX(1), RX(7)
RX(42) 3 K + 3 P + 3 AC ===> T



K



2 K



RX(2)

STAGE(1)
RGT M 1310-73-2 NaOH
SOL 7732-18-5 Water, 67-56-1 MeOH
CON 35 deg C

STAGE(2)
RCT K 75330-75-5
CON 35 deg C

STAGE(3)
SOL 7732-18-5 Water
CON 35 deg C, 8 atm

PRO L 75225-51-3
NTE reactant added in portions alternating with water over 2 h

RX(3) RCT L 75225-51-3

STAGE(1)
SOL 7732-18-5 Water
CON 35 deg C

STAGE(2)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
SOL 7732-18-5 Water
CON 35 deg C

STAGE(3)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON 35 deg C

STAGE(4)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, 35 deg C, pH 9.5

STAGE(5)
RGT O 7647-01-0 HCl
SOL 7732-18-5 Water

```
            CON  pH 4.4

          STAGE(6)
            RGT  O 7647-01-0 HCl
            SOL  7732-18-5 Water
            CON  0.5 hours, pH 2.5

        PRO  N 132748-10-8
        NTE  biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by
             SEQ ID NO:3)]; second and third stages buffer; fourth stage
             DASGIP AG-PRO bioreactor pH maintenance; reaction monitored by
             HPLC

RX(4)   RCT  N 132748-10-8

          STAGE(1)
            SOL  75-09-2 CH2Cl2
            CON  room temperature

          STAGE(2)
            CAT  1122-58-3 4-DMAP
            CON  room temperature

          STAGE(3)
            RCT  P 108-24-7
            CON  8.5 hours, room temperature

          STAGE(4)
            CAT  1122-58-3 4-DMAP
            CON  11 hours, room temperature

          STAGE(5)
            SOL  7732-18-5 Water
            CON  room temperature

        PRO  Q 145576-24-5
        NTE  last stage quench; reaction monitored by HPLC

RX(8)   RCT  Q 145576-24-5

          STAGE(1)
            SOL  110-86-1 Pyridine

          STAGE(2)
            CAT  1122-58-3 4-DMAP
            SOL  110-86-1 Pyridine

          STAGE(3)
            RCT  AC 5856-77-9
            SOL  110-86-1 Pyridine

        PRO  A 145576-25-6
        NTE  third stage syringe pump

RX(1)   RCT  A 145576-25-6

          STAGE(1)
            RGT  E 126-72-7 1-Propanol, 2,3-dibromo-, 1,1',1''-phosphate
            SOL  7732-18-5 Water, 67-56-1 MeOH
            CON  room temperature
```

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B 79902-63-9, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

RX(7) RCT B 79902-63-9

STAGE(1)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water, 67-56-1 MeOH

STAGE(2)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON 48 hours, pH 9 - 9.5

STAGE(3)
RGT AA 13968-08-6 Hydronium (H3O+)
SOL 7732-18-5 Water
CON pH 2

STAGE(4)
SOL 108-21-4 Acetic acid, 1-methylethyl ester
CON reflux

PRO T 79952-42-4
NTE biotransformation, enzymic [hydrolase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first two stages buffer; last stage Dean-Stark trap

IN Morgan, Brian; Burk, Mark; Levin, Michael; Zhu, Zoulin; Chaplin, Jennifer; Kustedjo, Karen ; Huang, Zilin; Greenberg, William
PA Diversa Corporation, USA

=> d ibib ed abs hitind hitstr 2
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, CASREACT' - CONTINUE? (Y)/N:y

L151 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:316955 HCAPLUS Full-text
DOCUMENT NUMBER: 144:369813
TITLE: The process for preparation of Simvastatin

INVENTOR(S): Ye, Hongping; Sun, Meng; Zhu, Zuolin
PATENT ASSIGNEE(S): Huaibei Huike Pharmaceutical, Co., Ltd., Peop. Rep. China
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006034641	A1	20060406	WO 2005-CN1572	20050926
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CN 1754870	A	20060405	CN 2004-10084820	20040930
US 20090043115	A1	20090212	US 2008-576424	20080222

PRIORITY APPLN. INFO.: CN 2004-10084820 A 20040930
WO 2005-CN1572 W 20050926

ED Entered STN: 06 Apr 2006
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention discloses a process for preparing Simvastatin and intermediate. Simvastatin was synthesized from Lovastatin via inorg. base hydrolysis to form the corresponding trihydroxy carboxylic acid I, then esterification with 2,2-dimethylbutanoyl chloride and catalytic ring opening to obtain II, further catalyzed by methylamine, or enzyme and acidification to provide the title product. An alternative process is protect the two hydroxy group on the side chain of Lovastatin hydrolysis compound I with 2,2-dimethoxypropane to give corresponding ketal, then esterification with 2,2-dimethylbutanoyl chloride, further acidic catalytic deprotection and cyclization to obtain the title product. The present invention uses inexpensive and available reagent, its condition is mild, and it leaves out the protective and deprotective steps which are necessary in prior methods. Compared with prior process, the esterification condition at 8-position is greatly simplified.

CC 26-6 (Biomolecules and Their Synthetic Analogs)
ST Simvastatin synthesis Lovastatin hydrolysis esterification cyclization
IT Cyclization
Esterification
Hydrolysis
(synthesis of Simvastatin from Lovastatin)
IT 77-76-9, 2,2-Dimethoxypropane 5856-77-9, 2,2-Dimethylbutanoyl chloride 75330-75-5, Lovastatin

RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of Simvastatin from Lovastatin)

IT 132748-10-8P 272456-96-9P 272456-97-0P 851402-85-2P
882025-44-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of Simvastatin from Lovastatin)

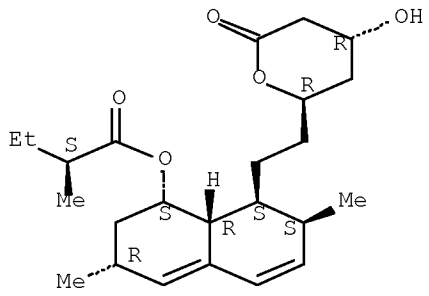
IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of Simvastatin from Lovastatin)

IT 75330-75-5, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of Simvastatin from Lovastatin)

RN 75330-75-5 HCAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (CA INDEX NAME)

Absolute stereochemistry.

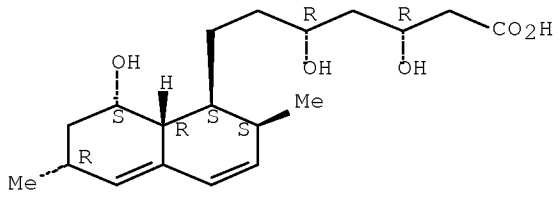


IT 132748-10-8P 851402-85-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of Simvastatin from Lovastatin)

RN 132748-10-8 HCAPLUS

CN 1-Naphthaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,8-trihydroxy-2,6-dimethyl-, (βR,δR,1S,2S,6R,8S,8aR)- (CA INDEX NAME)

Absolute stereochemistry.

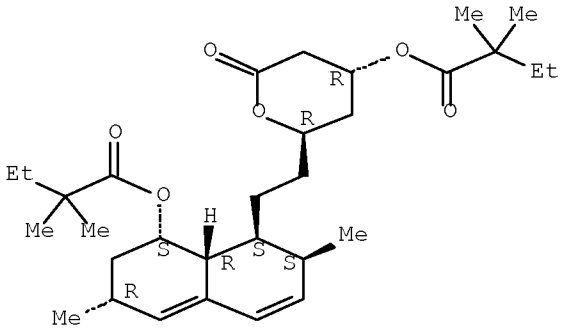


RN 851402-85-2 HCAPLUS

CN Butanoic acid, 2,2-dimethyl-, (2R,4R)-2-[2-[(1S,2S,6R,8S,8aR)-8-(2,2-

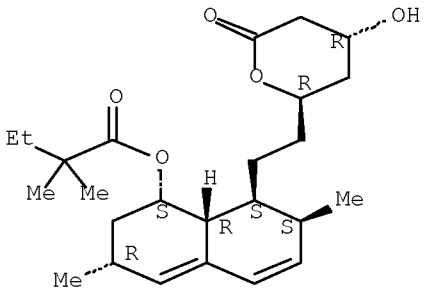
dimethyl-1-oxobutoxy)-1,2,6,7,8,8a-hexahydro-2,6-dimethyl-1-naphthalenyl]ethyl]tetrahydro-6-oxo-2H-pyran-4-yl ester (CA INDEX NAME)

Absolute stereochemistry.



IT 79902-63-9P, Simvastatin
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of Simvastatin from Lovastatin)
RN 79902-63-9 HCAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file stnguide
FILE 'STNGUIDE' ENTERED AT 11:13:22 ON 23 JUN 2009
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jun 19, 2009 (20090619/UP).

```
=> d his ful

     (FILE 'HOME' ENTERED AT 08:50:21 ON 23 JUN 2009)

     FILE 'STNGUIDE' ENTERED AT 08:50:24 ON 23 JUN 2009

     FILE 'HCAPLUS' ENTERED AT 08:50:44 ON 23 JUN 2009
                ACT CHA122HCAAPP/A
                ---------
L1              1 SEA SPE=ON  ABB=ON  PLU=ON  US2007-576122/APPS
                ---------

     FILE 'WPIX' ENTERED AT 08:51:05 ON 23 JUN 2009
                ACT CHA122WPIAPP/A
                ---------
L2              1 SEA SPE=ON  ABB=ON  PLU=ON  US2007-576122/APPS
                ---------

     FILE 'REGISTRY' ENTERED AT 08:51:28 ON 23 JUN 2009
                ACT CHA122REGAPP/A
                ---------
L3  (           1)SEA SPE=ON  ABB=ON  PLU=ON  US2007-576122/APPS
L4                SEL PLU=ON  L3 1- RN :      30 TERMS
L5             30 SEA SPE=ON  ABB=ON  PLU=ON  L4
                ---------
                ACT CHA122PSET1/A
                ---------
L6                STR
L7           5368 SEA SSS FUL L6
                ---------
L8              9 SEA SPE=ON  ABB=ON  PLU=ON  L5 AND MAN/CI
L9              3 SEA SPE=ON  ABB=ON  PLU=ON  L8 NOT SEQUENCE/FS
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 08:53:03 ON 23 JUN 2009

     FILE 'LREGISTRY' ENTERED AT 08:54:30 ON 23 JUN 2009
                ACT CHA122PSTRA/Q
                ---------
L10               STR
                ---------
                D QUE

     FILE 'LREGISTRY' ENTERED AT 08:55:16 ON 23 JUN 2009
L11               STR L10

     FILE 'REGISTRY' ENTERED AT 08:55:41 ON 23 JUN 2009
L12            50 SEA SUB=L7 SSS SAM L11

     FILE 'LREGISTRY' ENTERED AT 08:57:48 ON 23 JUN 2009
L13               STR L11

     FILE 'REGISTRY' ENTERED AT 08:58:48 ON 23 JUN 2009
L14             9 SEA SUB=L7 SSS SAM L13
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 08:59:21 ON 23 JUN 2009
                D QUE STAT
```

```
     FILE 'REGISTRY' ENTERED AT 09:02:04 ON 23 JUN 2009
L15         199 SEA SUB=L7 SSS FUL L13
                SAVE TEMP L15 CHA122PSETA/A

     FILE 'LREGISTRY' ENTERED AT 09:03:16 ON 23 JUN 2009
L16             STR L13

     FILE 'REGISTRY' ENTERED AT 09:04:45 ON 23 JUN 2009
L17          11 SEA SUB=L7 SSS SAM L16

     FILE 'STNGUIDE' ENTERED AT 09:05:46 ON 23 JUN 2009
                D QUE STAT

     FILE 'REGISTRY' ENTERED AT 09:07:51 ON 23 JUN 2009
L18         202 SEA SUB=L7 SSS FUL L16
                SAVE TEMP L18 CHA122PSETE/A

     FILE 'STNGUIDE' ENTERED AT 09:08:45 ON 23 JUN 2009

     FILE 'LREGISTRY' ENTERED AT 09:10:21 ON 23 JUN 2009
L*** DEL         STR L6
                 ACT CHA122PSTRB/Q
                ---------
L19              STR
                ---------
L20              STR L19

     FILE 'REGISTRY' ENTERED AT 09:12:20 ON 23 JUN 2009
L21            3 SEA SUB=L7 SSS SAM L20
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 09:13:01 ON 23 JUN 2009
                D QUE STAT

     FILE 'REGISTRY' ENTERED AT 09:15:06 ON 23 JUN 2009
L22          18 SEA SUB=L7 SSS FUL L20
                SAVE TEMP L22 CHA122PSETB/A

     FILE 'STNGUIDE' ENTERED AT 09:16:38 ON 23 JUN 2009

     FILE 'LREGISTRY' ENTERED AT 09:17:20 ON 23 JUN 2009
                 ACT CHA122PSTRC/Q
                ---------
L23              STR
                ---------
L24              STR L23

     FILE 'REGISTRY' ENTERED AT 09:17:54 ON 23 JUN 2009
L25            0 SEA SUB=L7 SSS SAM L24

     FILE 'STNGUIDE' ENTERED AT 09:18:10 ON 23 JUN 2009
                D QUE STAT

     FILE 'REGISTRY' ENTERED AT 09:20:18 ON 23 JUN 2009
L26            5 SEA SUB=L7 SSS FUL L24
                 SAVE TEMP L26 CHA122PSETC/A
                 D SCAN

     FILE 'LREGISTRY' ENTERED AT 09:21:19 ON 23 JUN 2009
                 ACT CHA122PSTRD/Q
```

```
              ---------
L27            STR
              ---------
L28            STR L27

     FILE 'REGISTRY' ENTERED AT 09:22:07 ON 23 JUN 2009
L29          50 SEA SUB=L7 SSS SAM L28

     FILE 'STNGUIDE' ENTERED AT 09:22:38 ON 23 JUN 2009
               D QUE STAT

     FILE 'REGISTRY' ENTERED AT 09:24:51 ON 23 JUN 2009
L30         800 SEA SUB=L7 SSS FUL L28
               SAVE TEMP L30 CHA122PSETD/A

     FILE 'STNGUIDE' ENTERED AT 09:25:43 ON 23 JUN 2009

     FILE 'STNGUIDE' ENTERED AT 10:15:16 ON 23 JUN 2009

     FILE 'ZCAPLUS' ENTERED AT 10:15:26 ON 23 JUN 2009
L31            QUE SPE=ON  ABB=ON  PLU=ON  MORGAN, B?/AU,AUTH
L32            QUE SPE=ON  ABB=ON  PLU=ON  BURK, M?/AU,AUTH
L33            QUE SPE=ON  ABB=ON  PLU=ON  LEVIN, M?/AU,AUTH
L34            QUE SPE=ON  ABB=ON  PLU=ON  ZHU, Z?/AU,AUTH
L35            QUE SPE=ON  ABB=ON  PLU=ON  CHAPLIN, J?/AU,AUTH
L36            QUE SPE=ON  ABB=ON  PLU=ON  KUSTEDJO, K?/AU,AUTH
L37            QUE SPE=ON  ABB=ON  PLU=ON  HUANG, Z?/AU,AUTH
L38            QUE SPE=ON  ABB=ON  PLU=ON  GREENBERG, W?/AU,AUTH
L39            QUE SPE=ON  ABB=ON  PLU=ON  GREENBERG, B?/AU,AUTH
L40            QUE SPE=ON  ABB=ON  PLU=ON  (DIVERSA OR VERENIUM)/CS,SO,PA
L41            QUE SPE=ON  ABB=ON  PLU=ON  LOVASTATIN
L42            QUE SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN
L43            QUE SPE=ON  ABB=ON  PLU=ON  (4(1W)ACETYL)(3A)L42
L44            QUE SPE=ON  ABB=ON  PLU=ON  ENZYM?
L45            QUE SPE=ON  ABB=ON  PLU=ON  HYDROLY?
L46            QUE SPE=ON  ABB=ON  PLU=ON  LACTONIS? OR LACTONIZ?
L47            QUE SPE=ON  ABB=ON  PLU=ON  ACYLAT?
L48            QUE SPE=ON  ABB=ON  PLU=ON  HYDROLYSIS+PFT,OLD,NEW,NT/CT
L49            QUE SPE=ON  ABB=ON  PLU=ON  LACTONIZATION+PFT,OLD,NEW,NT/CT
L50            QUE SPE=ON  ABB=ON  PLU=ON  ACETYLATION+PFT,OLD,NEW,NT/CT
L51            QUE SPE=ON  ABB=ON  PLU=ON  ACYLATION+PFT,OLD,NEW,NT/CT
L52            QUE SPE=ON  ABB=ON  PLU=ON  DEACETYLATION+PFT,OLD,NEW,NT/CT
L53            QUE SPE=ON  ABB=ON  PLU=ON  DEACYLATION+PFT,OLD,NEW,NT/CT
L54            QUE SPE=ON  ABB=ON  PLU=ON  SYNTH OR SYNTHES? OR SYNTHETIC? OR
               PRODUC? OR MANUFACT? OR PREP OR PREPAR? OR YIELD? OR MAKE OR
               MAKING OR MADE OR PROCESS? OR GIVE OR GIVING OR GAVE OR
               FORMING OR FORM OR FORMATION OR FORMS OR FORMED

     FILE 'HCAPLUS' ENTERED AT 10:23:16 ON 23 JUN 2009
L55         5405 SEA SPE=ON  ABB=ON  PLU=ON  L18
L56          159 SEA SPE=ON  ABB=ON  PLU=ON  L55 (L)(PREP+NT)/RL
L57         4264 SEA SPE=ON  ABB=ON  PLU=ON  L15
L58          162 SEA SPE=ON  ABB=ON  PLU=ON  L57 (L)(RACT+NT)/RL
L59           69 SEA SPE=ON  ABB=ON  PLU=ON  L56 AND L58
L60           26 SEA SPE=ON  ABB=ON  PLU=ON  L22
L61            3 SEA SPE=ON  ABB=ON  PLU=ON  L26
L62           40 SEA SPE=ON  ABB=ON  PLU=ON  L30
L63            9 SEA SPE=ON  ABB=ON  PLU=ON  L59 AND (L60 OR L61 OR L62)
L64           13 SEA SPE=ON  ABB=ON  PLU=ON  L59 AND L49
L65        17587 SEA SPE=ON  ABB=ON  PLU=ON  L9
```

```
L66           1 SEA SPE=ON  ABB=ON  PLU=ON  L59 AND L9
L67           1 SEA SPE=ON  ABB=ON  PLU=ON  L59 AND (L48(L)L44)
L68          19 SEA SPE=ON  ABB=ON  PLU=ON  L63 OR L64 OR (L66 OR L67)
L69          19 SEA SPE=ON  ABB=ON  PLU=ON  L68 AND (L41 OR L42 OR L43 OR L44
                OR L45 OR L46 OR L47 OR L48 OR L49 OR L50 OR L51 OR L52 OR
                L53)
L70          19 SEA SPE=ON  ABB=ON  PLU=ON  L68 OR L69
                D SCAN TI HIT
L71           2 SEA SPE=ON  ABB=ON  PLU=ON  L70 AND (L31 OR L32 OR L33 OR L34
                OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L72          17 SEA SPE=ON  ABB=ON  PLU=ON  L70 NOT L71

     FILE 'STNGUIDE' ENTERED AT 10:27:59 ON 23 JUN 2009

     FILE 'REGISTRY' ENTERED AT 10:28:01 ON 23 JUN 2009
L73         823 SEA SPE=ON  ABB=ON  PLU=ON  L22 OR L26 OR L30

     FILE 'CASREACT' ENTERED AT 10:28:33 ON 23 JUN 2009
L74          59 SEA SPE=ON  ABB=ON  PLU=ON  L18/PRO
L75          67 SEA SPE=ON  ABB=ON  PLU=ON  L15/NPRO
L76          34 SEA SPE=ON  ABB=ON  PLU=ON  L74 AND L75
L77           8 SEA SPE=ON  ABB=ON  PLU=ON  L22
L78           6 SEA SPE=ON  ABB=ON  PLU=ON  L76 AND L77
L79           9 SEA SPE=ON  ABB=ON  PLU=ON  L73
L80           6 SEA SPE=ON  ABB=ON  PLU=ON  L78 AND L79
                D SCAN
L81           1 SEA SPE=ON  ABB=ON  PLU=ON  L80 AND (L31 OR L32 OR L33 OR L34
                OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L82           5 SEA SPE=ON  ABB=ON  PLU=ON  L80 NOT L81
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 10:31:23 ON 23 JUN 2009

     FILE 'WPIX' ENTERED AT 10:33:09 ON 23 JUN 2009
                SEL L2 1- DCR
L83           6 SEA SPE=ON  ABB=ON  PLU=ON  (DCR-101196/AN.S OR DCR-107036/AN.S
                 OR DCR-1074530/AN.S OR DCR-1074533/AN.S OR DCR-1074538/AN.S
                OR DCR-99623/AN.S OR 101196-K/AN.S OR 101196-P/AN.S OR
                107036-K/AN.S OR 107036-P/AN.S OR 107036-T/AN.S OR 1074530-K/AN
                .S OR 1074530-P/AN.S OR 1074533-K/AN.S OR 1074533-P/AN.S OR
                1074538-K/AN.S OR 1074538-P/AN.S OR 99623-K/AN.S OR 99623-S/AN.
                S)
                D TRI 1-6
                E LOVASTATIN/CN
L84           1 SEA SPE=ON  ABB=ON  PLU=ON  LOVASTATIN/CN
                D IDE
L85          97 SEA SPE=ON  ABB=ON  PLU=ON  99623/DCSE
L86        1315 SEA SPE=ON  ABB=ON  PLU=ON  R16653/DCN OR R19716/DCN OR
                L85/DCR OR L84/DCR
L87          36 SEA SPE=ON  ABB=ON  PLU=ON  L86(T)(S OR RCT)/DCN,DCR
                E SIMVASTATIN/CN
L88           1 SEA SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN/CN
                D IDE
L89           5 SEA SPE=ON  ABB=ON  PLU=ON  107036/DCSE
L90        1291 SEA SPE=ON  ABB=ON  PLU=ON  L88/DCR OR L89/DCR OR R16884/DCN
L91          87 SEA SPE=ON  ABB=ON  PLU=ON  L90 (T) (P OR PRD)/DCN,DCR
L92          21 SEA SPE=ON  ABB=ON  PLU=ON  L87 AND L91
L93           8 SEA SPE=ON  ABB=ON  PLU=ON  L92 AND L46
L94           4 SEA SPE=ON  ABB=ON  PLU=ON  L93 AND (L47 OR DEACYL?/BIX,BIEX,AB
                EX,TT OR ACETYLAT?/BIX,BIEX,ABEX,TT OR DEACETYLAT?/BIX,BIEX,ABE
```

```
                X,TT)
L95             8 SEA SPE=ON  ABB=ON  PLU=ON  (L93 OR L94)
L96             8 SEA SPE=ON  ABB=ON  PLU=ON  L95 AND (L41 OR L42 OR L43 OR L44
                  OR L45 OR L46 OR L47)
L97             8 SEA SPE=ON  ABB=ON  PLU=ON  L95 AND L54
L98             8 SEA SPE=ON  ABB=ON  PLU=ON  (L95 OR L96 OR L97)
L99             1 SEA SPE=ON  ABB=ON  PLU=ON  L98 AND (L31 OR L32 OR L33 OR L34
                  OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L100            7 SEA SPE=ON  ABB=ON  PLU=ON  L98 NOT L99

     FILE 'STNGUIDE' ENTERED AT 10:41:37 ON 23 JUN 2009

     FILE 'CHEMINFORMRX' ENTERED AT 10:41:47 ON 23 JUN 2009
L101            1 SEA SPE=ON  ABB=ON  PLU=ON  L15
L102            0 SEA SPE=ON  ABB=ON  PLU=ON  L18

     FILE 'STNGUIDE' ENTERED AT 10:42:28 ON 23 JUN 2009

     FILE 'MEDLINE' ENTERED AT 10:43:00 ON 23 JUN 2009
L103         3947 SEA SPE=ON  ABB=ON  PLU=ON  L18
                  E SIMVASTATIN/CT
L104              QUE SPE=ON  ABB=ON  PLU=ON  SIMVASTATIN+PFT,OLD,NEW,NT/CT
                  (P)CS/CT
L105         3692 SEA SPE=ON  ABB=ON  PLU=ON  L15
                  E LOVASTATIN/CT
                  E E58+ALL
L106         3947 SEA SPE=ON  ABB=ON  PLU=ON  L103 OR L104
L107              QUE SPE=ON  ABB=ON  PLU=ON  LOVASTATIN+PFT,OLD,NEW,NT/CT (P)
                  CH/CT
L108         3733 SEA SPE=ON  ABB=ON  PLU=ON  L105 OR L107
L109         1133 SEA SPE=ON  ABB=ON  PLU=ON  L106 AND L108
L110            2 SEA SPE=ON  ABB=ON  PLU=ON  L109 AND L104
                  D TRI 1-2
L111            2 SEA SPE=ON  ABB=ON  PLU=ON  L109 AND L46
L112            4 SEA SPE=ON  ABB=ON  PLU=ON  (L110 OR L111)
L113            4 SEA SPE=ON  ABB=ON  PLU=ON  L112 AND (L41 OR L42 OR L43 OR L44
                  OR L45 OR L46 OR L47)
L114            4 SEA SPE=ON  ABB=ON  PLU=ON  L112 OR L113
L115            0 SEA SPE=ON  ABB=ON  PLU=ON  L114 AND (L31 OR L32 OR L33 OR L34
                  OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L116            4 SEA SPE=ON  ABB=ON  PLU=ON  L114 NOT L115

     FILE 'STNGUIDE' ENTERED AT 10:47:23 ON 23 JUN 2009

     FILE 'EMBASE' ENTERED AT 10:48:02 ON 23 JUN 2009
L117        15476 SEA SPE=ON  ABB=ON  PLU=ON  L18
L118          381 SEA SPE=ON  ABB=ON  PLU=ON  L54(5A)(L42 OR L43)
L119         9261 SEA SPE=ON  ABB=ON  PLU=ON  L15
L120           67 SEA SPE=ON  ABB=ON  PLU=ON  L118 AND L119
L121            2 SEA SPE=ON  ABB=ON  PLU=ON  L120 AND L46
                  D TRI 1-2
L122         4661 SEA SPE=ON  ABB=ON  PLU=ON  L117 AND L119
L123            0 SEA SPE=ON  ABB=ON  PLU=ON  L73
L124           65 SEA SPE=ON  ABB=ON  PLU=ON  L122 AND (L123 OR L118)
L125           15 SEA SPE=ON  ABB=ON  PLU=ON  L124 AND (L46 OR LACTONE)
L126            0 SEA SPE=ON  ABB=ON  PLU=ON  L125 AND (L47 OR ACETYLAT? OR
                  DEACYL? OR DEACETYL?)
L127           15 SEA SPE=ON  ABB=ON  PLU=ON  (L125 OR L126)
L128           15 SEA SPE=ON  ABB=ON  PLU=ON  L127 AND (L41 OR L42 OR L43 OR L44
                  OR L45 OR L46 OR L47)
```

```
L129         15 SEA SPE=ON  ABB=ON  PLU=ON  (L127 OR L128)
                D TRI 10-15
                D KWIC 15
L130          2 SEA SPE=ON  ABB=ON  PLU=ON  L129 AND L46
                D KWIC 1-2
L131          0 SEA SPE=ON  ABB=ON  PLU=ON  L130 AND (L31 OR L32 OR L33 OR L34
                OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L132          2 SEA SPE=ON  ABB=ON  PLU=ON  L130 NOT L131

     FILE 'STNGUIDE' ENTERED AT 10:52:43 ON 23 JUN 2009

     FILE 'BIOSIS, CABA, BIOTECHNO, DRUGU, VETU' ENTERED AT 10:53:32 ON 23 JUN
     2009
L133      10730 SEA SPE=ON  ABB=ON  PLU=ON  L18
L134       5907 SEA SPE=ON  ABB=ON  PLU=ON  L15
L135       1252 SEA SPE=ON  ABB=ON  PLU=ON  L133 AND L134
L136          0 SEA SPE=ON  ABB=ON  PLU=ON  L73
L137        100 SEA SPE=ON  ABB=ON  PLU=ON  (L54 (5A) L42) (8A) L41
L138         45 SEA SPE=ON  ABB=ON  PLU=ON  L135 AND ((L136 OR L137))
L139          1 SEA SPE=ON  ABB=ON  PLU=ON  L138 AND L46
                D SCAN
L140          1 SEA SPE=ON  ABB=ON  PLU=ON  L139 AND (L41 OR L42 OR L43 OR L44
                OR L45 OR L46 OR L47)
L141          1 SEA SPE=ON  ABB=ON  PLU=ON  L139 OR L140
L142          0 SEA SPE=ON  ABB=ON  PLU=ON  L141 AND (L31 OR L32 OR L33 OR L34
                OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L143          1 SEA SPE=ON  ABB=ON  PLU=ON  L141 NOT L142

     FILE 'STNGUIDE' ENTERED AT 10:56:32 ON 23 JUN 2009

     FILE 'PASCAL, JAPIO, LIFESCI, BIOENG, BIOTECHDS, DRUGB, VETB, SCISEARCH,
     CONFSCI, DISSABS, RDISCLOSURE' ENTERED AT 10:57:03 ON 23 JUN 2009
L144         77 SEA SPE=ON  ABB=ON  PLU=ON  (L54 (5A) L42) (8A) L41
L145          3 SEA SPE=ON  ABB=ON  PLU=ON  L144 AND L46
L146          3 SEA SPE=ON  ABB=ON  PLU=ON  L145 AND (L41 OR L42 OR L43 OR L44
                OR L45 OR L46 OR L47)
L147          3 SEA SPE=ON  ABB=ON  PLU=ON  (L145 OR L146)
L148          1 SEA SPE=ON  ABB=ON  PLU=ON  L147 AND (L31 OR L32 OR L33 OR L34
                OR L35 OR L36 OR L37 OR L38 OR L39 OR L40)
L149          2 SEA SPE=ON  ABB=ON  PLU=ON  L147 NOT L148
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 11:01:19 ON 23 JUN 2009
                D QUE STAT L7
                D QUE STAT L9
                D QUE STAT L15
                D QUE STAT L18
                D QUE STAT L22
                D QUE STAT L26
                D QUE STAT L30
                D QUE NOS L73
                D QUE NOS L82
                D QUE NOS L72
                D QUE NOS L102
                D QUE L100
                D QUE NOS L116
                D QUE NOS L132
                D QUE NOS L143
                D QUE NOS L149
```

```
     FILE 'CASREACT, HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, JAPIO, BIOTECHDS'
     ENTERED AT 11:04:41 ON 23 JUN 2009
L150         29 DUP REM L82 L72 L100 L102 L116 L132 L143 L149 (9 DUPLICATES REM
                    ANSWERS '1-5' FROM FILE CASREACT
                    ANSWERS '6-17' FROM FILE HCAPLUS
                    ANSWERS '18-20' FROM FILE WPIX
                    ANSWERS '21-24' FROM FILE MEDLINE
                    ANSWERS '25-26' FROM FILE EMBASE
                    ANSWER '27' FROM FILE BIOSIS
                    ANSWER '28' FROM FILE JAPIO
                    ANSWER '29' FROM FILE BIOTECHDS
               SAVE TEMP L150 CHA122MAINP/A

     FILE 'STNGUIDE' ENTERED AT 11:05:08 ON 23 JUN 2009

     FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE, BIOSIS, JAPIO, BIOTECHDS'
     ENTERED AT 11:05:41 ON 23 JUN 2009
               D IBIB ABS HIT

     FILE 'STNGUIDE' ENTERED AT 11:05:54 ON 23 JUN 2009

     FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE, BIOSIS, JAPIO, BIOTECHDS'
     ENTERED AT 11:06:05 ON 23 JUN 2009
               D IBIB ABS HIT 2-5

     FILE 'STNGUIDE' ENTERED AT 11:06:52 ON 23 JUN 2009

     FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE, BIOSIS, JAPIO, BIOTECHDS'
     ENTERED AT 11:07:08 ON 23 JUN 2009
               D IBIB ED ABS HITIND HITSTR 6-17

     FILE 'STNGUIDE' ENTERED AT 11:07:12 ON 23 JUN 2009

     FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE, BIOSIS, JAPIO, BIOTECHDS'
     ENTERED AT 11:07:37 ON 23 JUN 2009
               D IALL ABEQ TECH ABEX FRAGHITSTR 18-20

     FILE 'STNGUIDE' ENTERED AT 11:07:38 ON 23 JUN 2009

     FILE 'HCAPLUS, CASREACT, WPIX, MEDLINE, EMBASE, BIOSIS, JAPIO, BIOTECHDS'
     ENTERED AT 11:08:17 ON 23 JUN 2009
               D IBIB ED AB IND 21-29

     FILE 'STNGUIDE' ENTERED AT 11:08:19 ON 23 JUN 2009
               D QUE NOS L81
               D QUE NOS L71
               D QUE L99
               D QUE NOS L115
               D QUE NOS L131
               D QUE NOS L142
               D QUE L148

     FILE 'CASREACT, HCAPLUS, WPIX, BIOTECHDS' ENTERED AT 11:10:12 ON 23 JUN
     2009
L151          2 DUP REM L81 L71 L99 L115 L131 L142 L148 (3 DUPLICATES REMOVED)
                    ANSWER '1' FROM FILE CASREACT
                    ANSWER '2' FROM FILE HCAPLUS
               SAVE TEMP L151 CHA122INV/A

     FILE 'STNGUIDE' ENTERED AT 11:10:25 ON 23 JUN 2009
```

```
FILE 'HCAPLUS, CASREACT' ENTERED AT 11:11:40 ON 23 JUN 2009
          D IBIB ABS HIT

FILE 'STNGUIDE' ENTERED AT 11:12:42 ON 23 JUN 2009

FILE 'HCAPLUS, CASREACT' ENTERED AT 11:13:05 ON 23 JUN 2009
          D IBIB ED ABS HITIND HITSTR 2

FILE 'STNGUIDE' ENTERED AT 11:13:06 ON 23 JUN 2009

FILE 'STNGUIDE' ENTERED AT 11:13:22 ON 23 JUN 2009


FILE HOME

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jun 19, 2009 (20090619/UP).

FILE HCAPLUS

Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 23 Jun 2009  VOL 150 ISS 26
FILE LAST UPDATED: 22 Jun 2009  (20090622/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Apr 2009

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE WPIX
FILE LAST UPDATED:          19 JUN 2009   <20090619/UP>
MOST RECENT UPDATE:           200939      <200939/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE
>>> Now containing more than 1.4 million chemical structures in DCR <<<

>>> IPC, ECLA and US National Classifications  have been updated
    with reclassifications to March 15th,  2009.
    F-Term and FI-Term original classifications are current and
    reclassification will commence in June.
    No update date (UP) has been created for the reclassified
    documents, but they can be identified by
    specific update codes (see HELP CLA for details)<<<
```

FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.com/stn_guide.html

FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomsonreuters.com/support/patents/coverage/latestupdate

EXPLORE DERWENT WORLD PATENTS INDEX IN STN ANAVIST, VERSION 2.0:
http://www.stn-international.com/DWPIAnaVist2_0608.html

>>> HELP for European Patent Classifications see HELP ECLA, HELP ICO <<<

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 22 JUN 2009 HIGHEST RN 1159446-15-7
DICTIONARY FILE UPDATES: 22 JUN 2009 HIGHEST RN 1159446-15-7

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 9, 2009.

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

FILE LREGISTRY
LREGISTRY IS A STATIC LEARNING FILE

CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

FILE ZCAPLUS

FILE COVERS 1907 - 23 Jun 2009 VOL 150 ISS 26
FILE LAST UPDATED: 22 Jun 2009 (20090622/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2009

ZCAplus now includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CASREACT

FILE CONTENT:1840 - 21 Jun 2009 VOL 150 ISS 26

New CAS Information Use Policies, enter HELP USAGETERMS for details.

****
*
* CASREACT now has more than 16.5 million reactions
*
****

CASREACT contains reactions from CAS and from: ZIC/VINITI database (1974-1999) provided by InfoChem; INPI data prior to 1986; Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich; organic reactions, portions copyright 1996-2006 John Wiley & Sons, Ltd., John Wiley and Sons, Inc., Organic Reactions Inc., and Organic Syntheses Inc. Reproduced under license. All Rights Reserved.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CHEMINFORMRX
FILE LAST UPDATED: 8 APR 2009 <20090408/UP>

>>> CAS Registry Numbers are available for
    substances prior to 1995 <<<

FILE MEDLINE
 FILE LAST UPDATED: 20 Jun 2009 (20090620/UP). FILE COVERS 1949 TO DATE.

 MEDLINE and LMEDLINE have been updated with the 2009 Medical Subject Headings (MeSH) vocabulary and tree numbers from the U.S. National Libra of Medicine (NLM). Additional information is available at

 http://www.nlm.nih.gov/pubs/techbull/nd08/nd08_medline_data_changes_2009.

 On February 21, 2009, MEDLINE was reloaded. See HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate substance identification.

 See HELP RANGE before carrying out any RANGE search.

FILE EMBASE
 FILE COVERS 1974 TO 23 Jun 2009 (20090623/ED)

 EMBASE was reloaded on March 30, 2008.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

Beginning January 2008, Elsevier will no longer provide EMTREE codes as part of the EMTREE thesaurus in EMBASE. Please update your current-awareness alerts (SDIs) if they contain EMTREE codes.

For further assistance, please contact your local helpdesk.

FILE BIOSIS
FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 17 June 2009 (20090617/ED)

BIOSIS has been augmented with 1.8 million archival records from 1926 through 1968. These records have been re-indexed to match current BIOSIS indexing.

FILE CABA
FILE COVERS 1973 TO 4 Jun 2009 (20090604/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

FILE BIOTECHNO
FILE LAST UPDATED: 7 JAN 2004 <20040107/UP>
FILE COVERS 1980 TO 2003.
THIS FILE IS A STATIC FILE WITH NO UPDATES

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN /CT AND BASIC INDEX <<<

FILE DRUGU
FILE LAST UPDATED: 17 JUN 2009 <20090617/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

FILE VETU
FILE LAST UPDATED: 2 JAN 2002 <20020102/UP>
FILE COVERS 1983-2001

FILE PASCAL
FILE LAST UPDATED: 22 JUN 2009 <20090622/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN THE BASIC INDEX (/BI) FIELD <<<

```
FILE JAPIO
FILE LAST UPDATED:            8 JUN 2009       <20090608/UP>
MOST RECENT PUBLICATION DATE: 26 FEB 2009       <20090226/PD>

>>> GRAPHIC IMAGES AVAILABLE <<<

FILE LIFESCI
FILE COVERS 1978 TO 1 May 2009 (20090501/ED)

FILE BIOENG
FILE LAST UPDATED: 3 JUN 2009       <20090603/UP>
FILE COVERS 1982 TO DATE

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN
    THE BASIC INDEX <<<

FILE BIOTECHDS
FILE LAST UPDATED: 19 JUN 2009       <20090619/UP>
FILE COVERS 1982 TO DATE

>>> USE OF THIS FILE IS LIMITED TO BIOTECH SUBSCRIBERS <<<


FILE DRUGB
 >>>  FILE COVERS 1964 TO 1982 - CLOSED FILE  <<<


FILE VETB
FILE LAST UPDATED: 25 SEP 94      <940925/UP>
FILE COVERS 1968-1982


FILE SCISEARCH

FILE COVERS 1974 TO 18 Jun 2009 (20090618/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE CONFSCI
FILE COVERS 1973 TO 30 Mar 2009 (20090330/ED)

CSA has resumed updates, see NEWS FILE

FILE DISSABS
FILE COVERS 1861 TO 28 MAY 2009 (20090528/ED)

Only fair use as provided by the United States copyright law is
permitted.  PROQUEST INFORMATION AND LEARNING COMPANY MAKES NO
WARRANTY REGARDING THE ACCURACY, COMPLETENESS OR TIMELINESS OF
THE LICENSED MATERIALS OR ANY WARRANTY, EXPRESS OR IMPLIED,
INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A
PARTICULAR PURPOSE, AND SHALL NOT BE LIABLE FOR DAMAGES OF ANY
KIND OR LOST PROFITS OR OTHER CLAIMS RELATED TO THE LICENSED
MATERIALS OR THEIR USE.

FILE RDISCLOSURE
FILE LAST UPDATED: 15 JUN 2009       <20090615/UP>
FILE COVERS 1960 TO DATE
```

```
      >>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN THE
          BASIC INDEX (/BI) AND TITLE (/TI) FIELDS <<<

      >>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=>
```